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OVARIAN DYSGERMINOMA

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The term dysgerminoma was introduced by Meyer to designate a rare type of ovarian tumor formerly referred to by a variety of names —seminoma, embryoma, sex cell carcinoma and large round cell sarcoma. A similar tumor occurring in the testis has been long recognized. Chenot in 1911 first called attention to the corresponding tumor in the ovary, although in this location its occurrence is far more infrequent. Chenot used the name seminoma because he considered the tumor to be derived from the anlage of the seminiferous tubules. Pick in 1912 described such a tumor as chorioepithelioma ectodermale; he concluded that it is teratoid and is derived from the cells of the chorionic villi. Meyer in 1925 made a comprehensive review of all the cases reported in the literature to that date and stressed that this tumor is the most frequent form found in the gonads of hermaphrodites and pseudohermaphrodites. Since the appearance of Meyer's paper many cases have been reported, the majority in the German literature. In the present paper 79 cases have been assembled from the literature, exclusive of 23 cases described by Meyer in which the patients were hermaphrodites or pseudohermaphrodites (table 1). Nineteen cases from the records of the Surgical Pathologic Laboratory are added (table 2).

No conclusions can be formed concerning the incidence of this type of tumor on the basis of the 19 cases, the present series, since these were not obtained from a routine gynecologic service. Klaften, from his studies of a series of 188 malignant ovarian tumors, estimated the incidence at about 3 per cent of all malignant ovarian tumors. Other observers have given an even lower frequency.

CLINICAL FEATURES

There are several clinical features which aid in arriving at a preoperative diagnosis of dysgerminoma. These include the duration of symptoms and the age and sexual development of the patient. The

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TABLE 1.—*Summary of Seventy-Nine Cases Recorded in the Literature*

Author	Patient's Age	Site of Involvement	Metastases	Children	Condition	Treatment	Postoperative Course
Babes	13	Bilateral	+	0	Hypoplastic uterus	?	?
Bonnet	17	Left ovary	Ascites; recurrence	0	0	Excision of tumor	Ascites; recurrence at 3 mo.
Döderlein	19	Right ovary	+ Omental	0	Normal	Right salpingo-oophorectomy 1935; resection of omentum 1936	Living at 1 yr.
Du Pont	54	Left ovary	0	0	No right ovary	Excision of tumor	?
Dworzak	18	Bilateral	?	0	Normal	Bilateral salpingo-oophorectomy; hysterectomy	Dead at ½ yr.
Dworzak	20	Right ovary	+	0	Normal	Salpingo-oophorectomy	Dead at 13 days
Dworzak	44	Right ovary	?	1	Normal	Bilateral salpingo-oophorectomy; hysterectomy	Dead at 2 yr.
Dworzak	37	Left ovary	+	?	Normal	?	Dead at 1½ yr.
Fauvet	33	Right ovary	0	1	Normal	Right salpingo-oophorectomy	?
Fauvet	34	Bilateral	+	3	Normal	?	Dead
Fauvet	19	Left ovary	?	0	Amenorrhea; hypoplastic uterus; no right ovary	?	Dead
Fauvet	20	Left ovary	0	0	Normal	?	?
Fauvet	52	Bilateral	+	2	Normal	Bilateral salpingo-oophorectomy	Died
Fauvet	47	Bilateral	Recurrence with ascites 2 years	8	Normal	Bilateral salpingo-oophorectomy; hysterectomy; roentgen therapy	?
Frankl	28	Right ovary	+	0	No periods; undeveloped sexually	Bilateral salpingo-oophorectomy; hysterectomy	?
Frankl	51	Left ovary	0	0	Normal	Left salpingo-oophorectomy	?
Gilliard	19	Left ovary	+	1 p.o.	Normal	Left salpingo-oophorectomy; roentgen therapy	Living at 10 yr.
Gilliard	29	Bilateral	+	?	?	Laparotomy; roentgen therapy	Living at 1 yr.
Gross	25	Right ovary	?	1	?	?	?
Hajek	12	Right ovary	0	0	Uterus and ovary infantile	Hysterectomy; right salpingo-oophorectomy; roentgen therapy	?
Hajek	17	Right ovary	0	0	Normal	Bilateral salpingo-oophorectomy; hysterectomy; roentgen therapy	Living at 23 mo.
Hammant and Cornil	16½	Right ovary	0	0	Normal	Salpingo-oophorectomy	Well at 7 mo.
Hoche	22	Right dermoid; left dysgerminoma	+	0	Normal	Right salpingo-oophorectomy May 1927; left salpingo-oophorectomy December 1927; roentgen therapy	Living at 3½ yr.
Keller	31	Bilateral	?	0	Hypertrophied clitoris; infantile uterus	?	?
Klaften	26	Bilateral	+	?	?	Bilateral salpingo-oophorectomy; hysterectomy	Dead at 2 mo.

TABLE 1.—*Summary of Seventy-Nine Cases Recorded in the Literature—Continued*

Author	Patient's Age	Site of Involvement	Metastases	Children	Condition	Treatment	Postoperative Course
Klaften	23	?	+	?	?	?	?
Klein	15	Right ovary	0	?	Normal	?	Dead at 5½ yr.
Klein	15	Left ovary	0	0	Normal	Bilateral salpingo-oophorectomy; hysterectomy	?
Klein	19	Right ovary; left ovary 2 years later	?	0	?	Right salpingo-oophorectomy; left salpingo-oophorectomy	Dead
Klein	24	Right ovary	0	0	Sterility	Extirpation of tumor; roentgen therapy	Living at 16 yr.
Klein	22	Left ovary	0	2 postoperatively	Periods in menarche 18 yr.	Right salpingo-oophorectomy	Living at 7 yr.
Klein	30	Bilateral	0	1	Normal	Bilateral salpingo-oophorectomy	Living at 1½ yr.
Klein	17	Left ovary	0	0	Amenorrhea 4 mo.	?	Living at 4 mo.
Laffont and Bonafos	21	Right ovary	+ Ascites	1	Normal	?	Died at 4 mo.
Lubarsh	13	Bilateral	+	0	No periods	None	Dead
Matsner	33	Right ovary	0	0	Hypoplastic uterus; aplastic ovary; no periods	?	Died at 18 days
Matsner	17	Right ovary	Ascites	0	Irregular periods	Bilateral salpingo-oophorectomy	Well at 1 yr.
Matsner	25	Right ovary; left ovary 6 mo. later	+	0	Normal	Right salpingo-oophorectomy 1923; left salpingo-oophorectomy 1924; hysterectomy	?
Masson and Desmarest	14	Left ovary	+	0	No periods	Salpingo-oophorectomy	Died at 48 hr.
Ménétrier, Peyson, Isch-Wall and Lory	45	Right ovary	0	0	Clitoris enlarged; left ovotestis; cord for uterus	Bilateral salpingo-oophorectomy	Well
Ménétrier, Peyson, Isch-Wall and Lory	54	Left testicles undescended	0	0	Pseudohermaphrodite	Excision of tumor; successfully treated by roentgen therapy 6 yr. later	Recurrence 6 yr. ago; well at 12 yr.
Meyer	15	Bilateral	0	0	Normal	Bilateral salpingo-oophorectomy	Living at 6 yr.
Meyer	16	Right ovary	0	0	Hypoplastic uterus; normal periods after operation	Right salpingo-oophorectomy	Living at 8 yr.
Meyer	28	Left ovary	0	0	Hypoplastic uterus; regular periods	Left salpingo-oopherectomy	Living at 4 yr.
Meyer	49	Left ovary	Liver	0	Never menstruated	Extirpation of tumor	Dead at 2 yr.
Meyer	16	Right overy	?	0	Aplasia of ovary and uterus; no menstrual periods	Laparotomy	?
Meyer (Marion)	36	Right ovary	?	0	Pseudohermaphrodite	Extirpation	?
Meyer	30	Right ovary	0	0	Left ovotestis	Exploratory laparotomy	?
Neumann	15	Right ovary	?	?	?	?	?
Neumann	22	Right ovary	0	0	Hypoplastic uterus	Right salpingo-oophorectomy	Living at 6 mo.
Neumann	22	Bilateral	0	0	Normal	Bilateral salpingo-oophorectomy	?
Pick	9	Right ovary	+	0	Normal	0	?

TABLE 1.—*Summary of Seventy-Nine Cases Recorded in the Literature—Continued*

Author	Patient's Age	Site of Involvement	Metastases	Children	Condition	Treatment	Postoperative Course
Reifferscheid	35	Right ovary	0	3 abortions	Normal	?	?
Reifferscheid	18	Right ovary	0	0	Normal	?	Well
Reifferscheid	17	Bilateral	0 Ascites	0	Normal	?	?
Reifferscheid	14	Left ovary	+	0	Normal	Roentgen therapy	Well at 4 mo.
Reifferscheid	20	Right ovary	0	0	Normal	?	Well at 2 yr.
Reifferscheid	19	Left ovary	0	0	Normal	Bilateral salpingo-oophorectomy	Well at 3 yr.
Rössle	10	Bilateral	+	0	Normal	?	?
Schiller	13½	Bilateral	0	0	Normal	Bilateral salpingo-oophorectomy; hysterectomy	Living at 8 yr.
Schiller	23	Bilateral	+	0	Infantile genitalia	Bilateral salpingo-oophorectomy; roentgen therapy; hysterectomy	Living at 2 mo.
Schiller	18	Right ovary	0	0	Irregular periods	Roentgen therapy	?
Schiller	18	?	0	0	?	?	?
Schiller	24	Bilateral	0	2	Normal	Laparotomy; roentgen therapy	Well
Schiller	16	Right ovary	0	1 p.o.	Normal	Right salpingo-oophorectomy	Living at 10 yr.
Schiller	14	Bilateral	0	0	No periods	Bilateral salpingo-oophorectomy; hysterectomy; roentgen therapy	Living at ½ yr.
Schiller	19	Right ovary	0	1 p.o.	Normal	Right salpingo-oophorectomy	Living at 2 yr.
Schiller	47	?	?	3	Normal	?	?
Schiller	65	?	?	1	Normal	?	?
Szathmáry	28	Right ovary	Infiltration, rectum	2	Normal	Bilateral salpingo-oophorectomy; hysterectomy	?
Szathmáry	17	Right ovary	0 Ascites	0	Normal; amenorrhea 3 mo.	Left salpingo-oophorectomy	Well at 9 yr.
Szathmáry	22	Left ovary ?	Infiltration, omentum	0	Normal	Exploratory laparotomy	?
Szathmáry	36	Right ovary	0	5	Normal pregnancy present	Right salpingo-oophorectomy	Well at 4 mo.
Szathmáry	20	Bilateral	Infiltration	1	Tuberculosis	Bilateral salpingo-oophorectomy; hysterectomy	?
Tietze	10	Left ovary	0	0	Two periods; ceased after extirpation	Left salpingo-oophorectomy	Living at 1 yr.
Wallis	17	Left ovary	0	0	Normal	?	Living at 4 wk.
Wolfe and Kaminester	13	Right ovary	+ Liver and kidney	0	Normal	Exploratory laparotomy	Died at 4 days
Zacharias	32	Undescended right testis	?	0	Female hermaphrodite	?	?
Zimmerman	17	Left ovary	0	0	Amenorrhea; normal periods after operation	Left salpingo-oophorectomy	Living at 1½ yr.
Zucker	26	?	+	0	Male hermaphrodite	?	Dead

TABLE 2.—*Summary of Nineteen Cases from the Records of the Surgical Pathologic Laboratory*

Patient	Age	Involvement	Metastases	Children	Condition	Treatment	Post-operative Course
20147	14	Left ovary	0	5 p.o.	Periods irregular 1 year, otherwise normal	Left salpingo-oophorectomy	Well at 20 yr.
15020	19	Right ovary	+ Bladder and rectum	0	Underdeveloped infantile uterus and left ovary; no periods	Bilateral salpingo-oophorectomy; hysterectomy	Dead at 11 mo.
37014	26	Left ovary	+ Recurrence	1	Normal	Left salpingo-oophorectomy; roentgen therapy	Well at 12 yr.
40452	13	Both ovaries	0	0	Normal	Bilateral salpingo-oophorectomy; hysterectomy	Well at 8 yr.
47822	39	Right testis	+ Recurrence	0	Male pseudo-hermaphrodite; no ovaries; testis undescended; tubes and uterus	Bilateral salpingectomy; hysterectomy; excision of tumor; roentgen therapy	Well at 5 yr.
57044	12	Right ovary	0 Ascites	0	?	Right salpingo-oophorectomy	Living at 4 mo.
57440	38	.....	0	10	Normal	Excision of tumor; roentgen therapy	Living at 2 yr.
57544	18	Right ovary	0	0*	Normal	Right salpingo-oophorectomy	Well at 4 mo.
.....	26	Left ovary	0	0	Normal	Left salpingo-oophorectomy; suspension of uterus; appendectomy	Well at 7 yr.
57550	28	Right ovary	0	0	Underdeveloped; amenorrhea 6 years; periods irregular at first	Exploratory laparotomy	Died at 4 days
57738	22	Right ovary	0	0	Advanced tuberculosis	Autopsy	Died from tuberculosis
40868	30	Right broad ligament	0 Recurrence	0	Female pseudo-hermaphrodite with reversion	Excision of tumor; roentgen therapy to recurrence	Died after 3 yr. from lobar pneumonia
32313	12	Right broad ligament	0	0	Normal	Excision of tumor; appendectomy	Well at 7½ yr.
57760	13	Right ovary	0	0	Normal; periods normal after operation	Right salpingo-oophorectomy	Living at 2 yr. 10 mo.
57900	34	Right ovary	0	1	Normal	?	?
58018	22	?	0	0	Normal	?	?
53016	31	Both ovaries	+	?	Normal	Laparotomy	Died at 1 mo.
57578	14	Left ovary	+ Uterus	0	Dysmenorrhea 4 mo.	Left salpingo-oophorectomy; roentgen therapy	Dead at 4 yr.
56320	28	Right ovary	+ Pancreas, liver, spleen, omentum, ascites	0	Normal	Right salpingo-oophorectomy	Died at 1 mo.

occurrence of a large, solid tumor in the right ovarian region in a girl past puberty is suggestive of such a diagnosis. The duration of abdominal pain and swelling (which are the leading symptoms) is usually about six months. Meyer has laid stress on the occurrence of dysgerminoma with pseudohermaphroditism, hypogenitalism and other forms of sexual maldevelopment, such as infantilism, amennorhea, delayed onset of menstruation and sterility. The absence of such abnormalities, however, is of no diagnostic significance. In 50 cases collected from the literature the tumor occurred in an otherwise normal person. Fifteen of 19 patients in the cases here reported had apparently normal external genitalia and secondary sexual characteristics. One showed infantilism, 2 were pseudohermaphrodites and another had amenorrhea. Patients with dysgerminoma are usually under 30 years of age; in the majority of cases in this series the tumor occurred while the patient was under 20 (table 3). This age distribution does not seem to apply in hermaphrodites and pseudohermaphrodites. Such patients are older. Dysgerminoma (seminoma) in the testis is most frequent after the age of 30 (Ferguson).

On palpation of the abdomen a tumor may be felt, which on pelvic examination gives the impression of a hard or elastic mass with an irregular nodular surface. Roentgenograms of the pelvis occasionally prove of value in differentiating such a tumor from a dermoid cyst or teratoma containing calcareous material.

Extensive infiltration of the rectum or the bladder with involvement of the retroperitoneal lymph nodes occurs with the more malignant tumors; however, metastasis to other organs is rare. In only 2 cases found in the literature was there metastasis elsewhere, in 1 case to the kidney and in the other to the liver. Aseites occurs in a small number of cases. In case 18 of the present series metastases were found in the spleen, the pancreas and the kidney. Metastasis to the lungs has not been reported.

Several observers have recently reported the presence of gonadotropic substances in the urine of patients with this type of ovarian tumor. However, quantitative assay has seldom been reported, and when the value has been given it has been under 200 rat units per liter. Wallis reported 150 to 200 mouse units per liter. Ferguson has reported higher values, 400 to 20,000 mouse units per liter, in 10 cases of seminoma of the testicle. The small amounts present in the urine and the rarity of the cases of ovarian dysgerminoma in which this test was performed make such a test of doubtful diagnostic value. In the case of Wallis the value was only slightly higher than that found at times in the urine of castrated persons or in urine obtained during the menopause.

No determinations have been made to indicate that the tumor itself secretes an endocrine substance. Assays on tumor tissue were found negative for gonadotropic substance by Zondek. He was unable to demonstrate any significant hormonal output in the urine of a patient with such a condition. In case 17 in the present series an Aschheim-Zondek test performed on the urine gave a negative result. Such assays should be carried out in all cases of suspected ovarian tumor, as only in this way will sufficient data be obtained to determine the significance of this test. Other endocrine studies, particularly assays of the blood and urine for estrogen, would be of interest because of the frequent associations of such tumors with sexual maldevelopment. In cases in which menstrual disturbances are present, low values for estrogen might be disclosed. The results of assays for androgen would be of interest also in cases in which the tumor is associated with hermaphroditism or pseudohermaphroditism.

TABLE 3.—*Age Incidence*

	Age					Total Cases
	0 to 9	10 to 19	20 to 29	30 to 39	40+	
Cases (Surg. path. lab.).....	0	8	6	5	0	19
Cases (literature).....	2	35	22	12	8	79
	2.5%	44.5%	28%	15%	10%	

PATHOLOGY

The outstanding gross pathologic features of this tumor are the firm or elastic consistency, the nodular surface and the large size (often in excess of 2,000 Gm.), suggesting rapid growth (fig. 1). The cut surface is granular and glistening, and the more dense stromatogeneous areas are widely separated. Microscopically the cells of the tumor stand out individually, suggesting the appearance of caviar, especially in the frozen section, in which phenomena of fixation play no part. The cells are large and discrete; they are arranged in nests and strands, with a moderate amount of clear cytoplasm which takes the eosin stain and with large hyperchromatic nuclei. In the better preserved cells nucleoli are a prominent feature. These features are well emphasized in figure 2. A characteristic arrangement in nests and strands is produced by the stroma, which forms a delicate network separating each cell and group of cells. With proper staining technic relatively large amounts of glycogen may be demonstrated in the cytoplasm (Döderlein). One of the more constant characteristics of the microscopic structure of these growths is the lymphoid infiltration of the stroma. The lymphoid nature of these cells, however, has not been fully established. Their minute size, the density of the chromatin in

them and the relative absence of cytoplasm suggest extruded polar bodies. The appearance of pseudotuberculosis, described by Schiller in 1936, was not present in the cases recorded in the surgical pathologic laboratory. In the present series of 19 cases the histologic picture has been uniform, unmixed with that of other types of tumor except in case 19. However, in 4 cases among those reviewed in the literature there was follicular arrangement resembling that of the granulosa cell tumor. Two of these cases were reported by Schiller, 1 by Reifferscheid and 1 by Babes. In a case reported by Hoche in 1930 the tumor was associated with a dermoid cyst, and in a case reported by Hartmann, Ménétrier and Isch-Wall dysgerminoma of the testis was associated with chorioepithelioma. In 3 cases which will be reported from the gynecologic service of the Johns Hopkins Hospital, there was a combination of dysgerminoma with malignant teratoma.

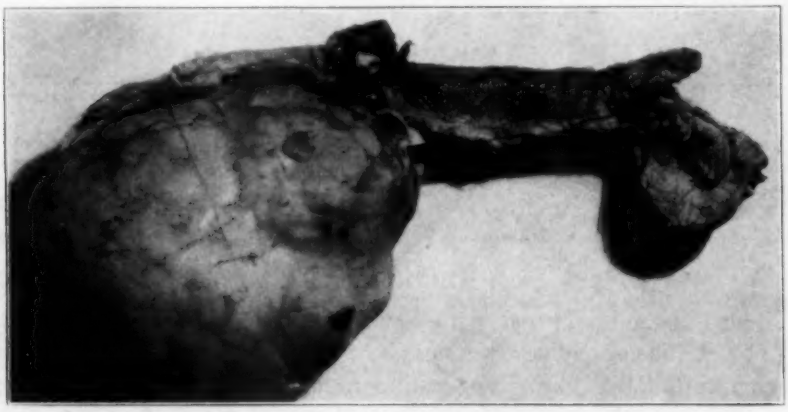

Fig. 1 (case 5).—Gross specimen of dysgerminoma occurring in a pseudohermaphrodite. Fallopian tubes, uterus and testes are present but there is no ovarian tissue outside the tumor. The patient is well five years after operation. For photomicrograph see figure 9.

In case 19 the bulk of the tumor was composed of primitive vascular tissue containing large cells, sometimes of epithelial appearance, with occasional giant cell formation and in other places containing spindle cells, such as those found in mesothelioma of the pleura (figs. 3 *A* and 3 *B*). Whether this tumor should be regarded as an example of dysgerminoma associated with chorioepithelioma, as reported by Hartmann, Ménétrier and Isch-Wall in a case of testicular tumor, or as a combination of dysgerminoma with a malignant tumor arising from undifferentiated elements of the ovarian stroma is not certain.

Malignant tumors of the retroperitoneal spaces, containing large cells suggesting those seen in dysgerminoma but with greater variation

in size and in staining reaction of both nucleus and cytoplasm, have been described. These tumors may also contain lymphoid stroma. It has been suggested by Schiller that such a tumor may be an ectopic dysgerminoma. However, such possible malignant variants cannot be properly classified with any degree of assurance, and they have been excluded from the present series.

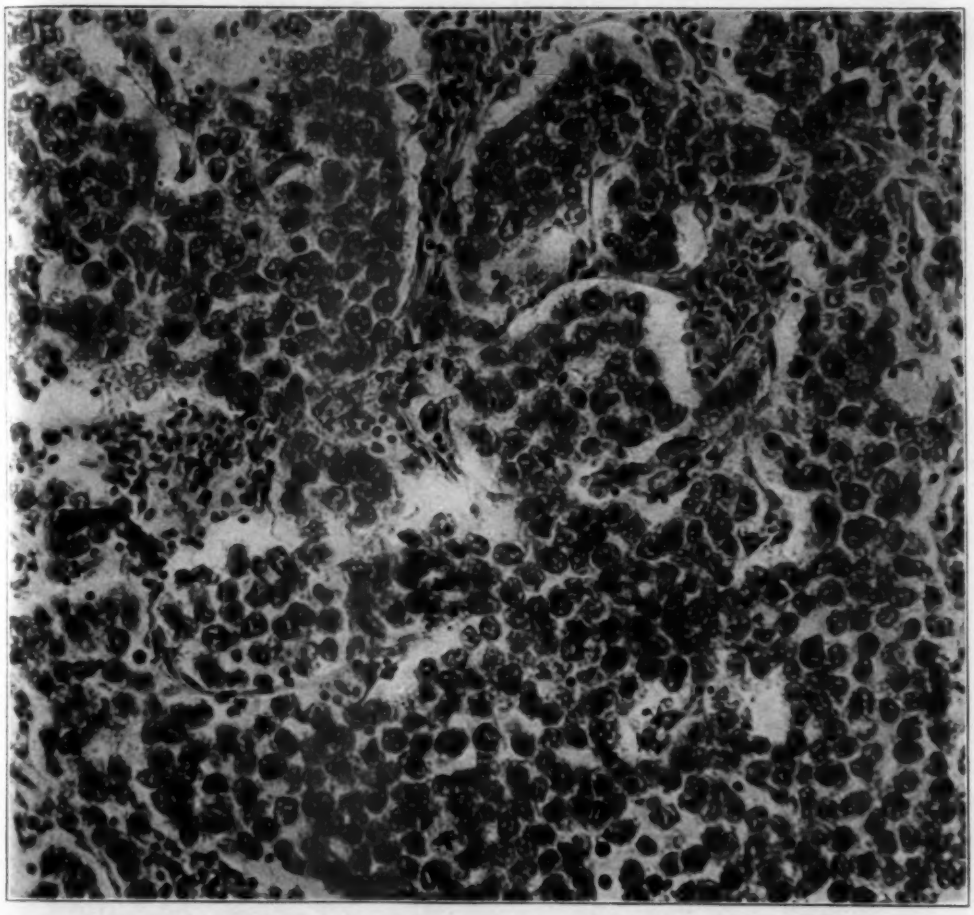

Fig. 2 (case 2).—Photomicrograph of a typical dysgerminoma, showing the caviar-like cells and lymphoid stroma. The tumor tissue is divided into nests or islands by delicate strands of connective tissue.

Uncertainty in regard to classification also applies to so-called senile dysgerminoma. This term has been applied to solid ovarian tumors containing cells resembling those found in typical dysgerminoma but without lymphoid stroma and occurring in elderly patients. Their atypical microscopic appearance and their occurrence in patients of advanced age have been attributed to slow and asymptomatic growth

over many years, which allows the tumor to remain latent and undiagnosed. Such an interpretation seems paradoxic, however, in view of the malignant clinical behavior of some of the tumors thus classified. Attempts to enlarge the dysgerminoma group by inclusion of histo-

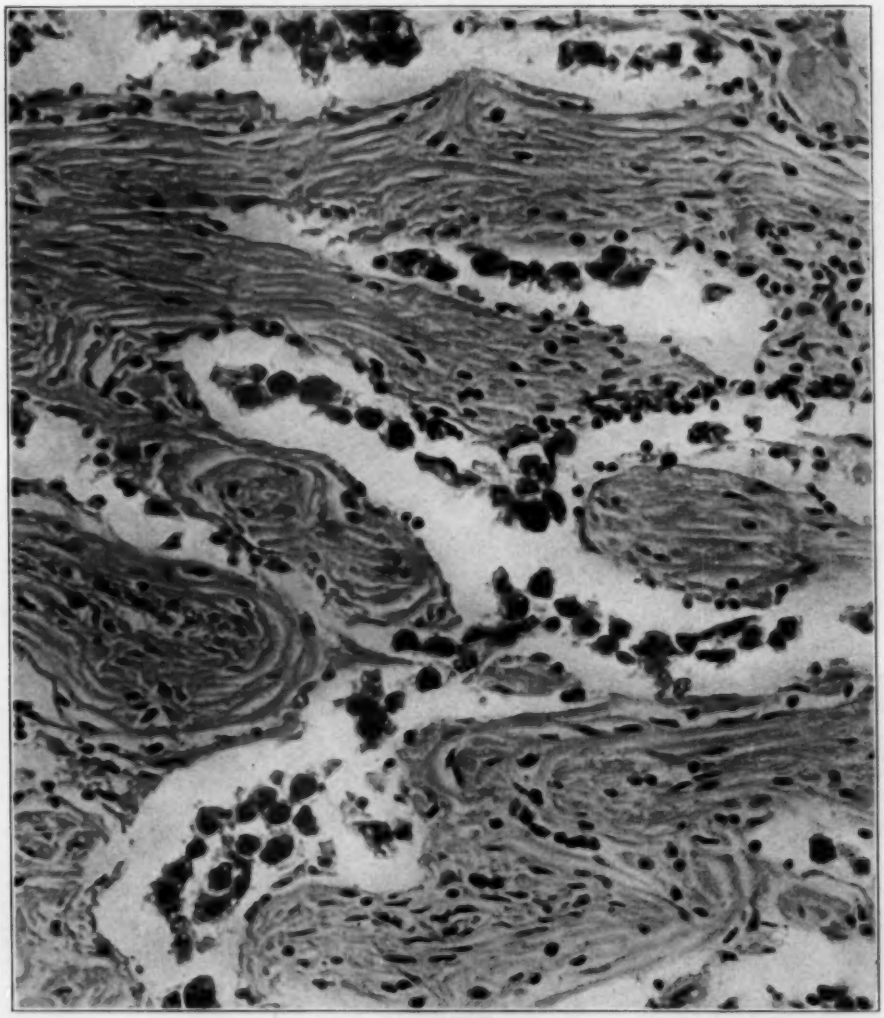

Fig. 3*A* (case 19).—Photomicrograph of a complex dysgerminoma, showing the histologic character of typical dysgerminoma.

logically atypical tumors can only lead to confusion, and in the present study all such histologic variants have been carefully excluded.

PROGNOSIS AND TREATMENT

The prognosis in cases of dysgerminoma is much disputed. On one hand, Meyer said the tumor is relatively benign, and on the other,

Klaften reported it as an "exquisite malignancy." This difference of opinion is partly due to the small series of cases reported by individual observers and the still smaller series of cases followed and partly due to the impossibility of differentiating the benign from the malignant

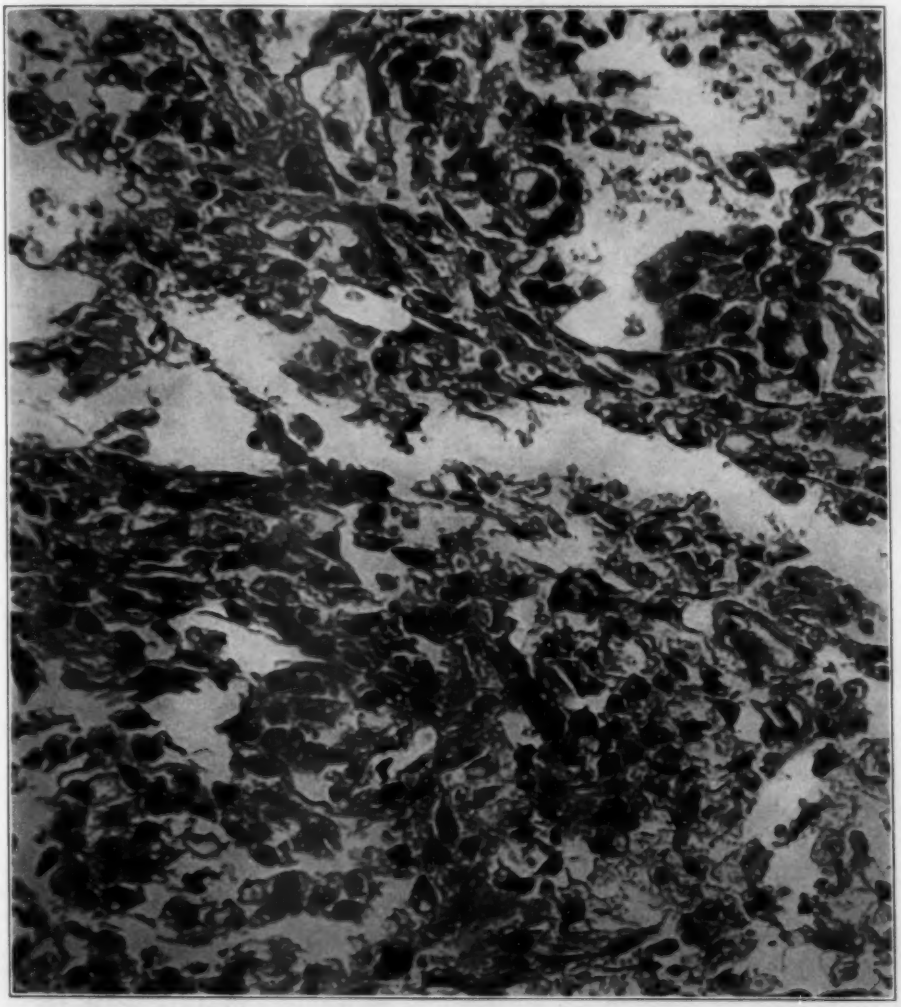

Fig. 3 *B*.—Photomicrograph showing the histologic character of another area of the tumor shown in figure 3 *A*, in which a mixture of large spindle cells and malignant epithelial cells suggests sarcoma of undifferentiated ovarian stroma or possibly chorionic tissue.

forms microscopically, a difficulty which is found frequently with all types of ovarian tumor. Fauvet, however, claimed to be able to give a correct prognosis on the basis of three criteria: (1) tumors found

at operation to be infiltrative and not discrete or associated with lymphatic metastasis are malignant; (2) the malignant tumor histologically shows extreme cellularity and paucity of connective tissue, and (3) the urine of patients with malignant dysgerminoma will give a positive reaction for gonadotropic substance.

Fauvet's first criterion is the most reliable, for in 17 cases of metastatic tumor reviewed in the literature in which the course of the process was adequately followed, 10 patients died, 6 were living after less than five years and only 1 was living after more than five years. In 4 of 7 cases of tumor with metastasis to the lymph nodes racorded in the surgical pathologic laboratory the growth was noted at operation to be infiltrative and the patient died. The patient in 1 of these cases (case 18) died in spite of roentgen therapy. In the other 3 cases there were recurrences in the lymph nodes after operation. In 1

TABLE 4.—*Lack of Correlation Between Clinical Results and Degree of Malignancy as Determined by Number of Mitoses*

Case No.	Number of Mitoses in 40 High Power Fields	Results
17	11	Died 1 month after operation
18	17	Died 4 years after operation
5	19	Well 5 years after operation
12	23	Died 3 years after operation, from lobar pneumonia
2	37	Died 11 months after operation
15	41	Not traced
11	41	Died from tuberculosis
14	41	Well 2 years and 10 months after operation
1	46	Well 20 years after operation
4	46	Well 8 years after operation
10	48	Died 4 days after operation
19	49	Died 1 month after operation
3	50	Well 12 years after operation
13	71	Well 7½ years after operation

of these complete cure followed postoperative roentgen therapy, and at the time of writing the patient has remained well for twelve years. In another the growth was arrested by implantation of radon; the patient was living and apparently well five years later. In the third case the condition responded to roentgen therapy; the patient lived three years, finally succumbing to lobar pneumonia.

In my experience, the degree of microscopic differentiation cannot be relied on in distinguishing a benign from a malignant tumor. The appearance of gonadotropic substance in the urine is likewise unreliable as a guide to prognosis, because of the scarcity of such determinations reported to date.

In 14 cases in the present series an attempt was made to distinguish benign from malignant dysgerminoma by counting the number of mitotic figures in forty successive high power fields (table 4). The results of these counts show that there is no correlation between the frequency of mitotic figures in the sections and the degree of malignancy of the tumor as shown by follow-up reports (figs. 4 and 5).

Of the cases in which there were adequate follow-up data, the patients in approximately 50 per cent have remained well beyond five years. Of 17 cases in which death was reported in the literature, in 5 it was postoperative and in 12 apparently from the effects of the tumor. Of 33 patients reported in the literature as living, only 10 were followed beyond five years. Of 19 patients studied by me 6 were living after five years, 4 were living under five years and 4 were dead from metastasis. Of the 4 remaining patients, 2 died from causes other than tumor, and 2 have not been traced (table 5).

The treatment of choice for dysgerminoma is excision of the tumor, the uterus and the opposite ovary being left intact. The preservation of the child-bearing function is desirable for the patients, who are usually young adults. For patients showing hermaphroditism or sexual underdevelopment the possibilty of future pregnancy is usually a consideration of no importance. For patients showing recurrence of the tumor in the regional lymph nodes after a primary excision, irradiation or a second excision is indicated.

TABLE 5.—*Mortality*

	Dead			Alive		
	Post-operative Deaths	Deaths from Tumor	Deaths from Other Causes	Under Five Years	Over Five Years	Not Traced
Cases (Surg. path. lab.).....	1	4	2	4	6	2
Cases (literature).....	5	12	?	23	10	29

In the advocacy of conservative surgical treatment for dysgerminoma the possibility of recurrence of the tumor in the opposite ovary must be considered. Only 2 cases of such involvement have been recorded in the literature. On the other hand, in 6 cases in which the affected ovary only was removed (5 reported by other authors and 1 in my own series) the patient subsequently gave birth to a healthy child. This would seem to warrant the slight risk of recurrence in the opposite ovary which is assumed when conservative excision is practiced.

Dysgerminoma of the ovary ranks with myeloid and lymphoid tumors in its radiosensitivity. Several authors, Gilliard (1 case) and Ménétrier, Peyron and others (2 cases), have reported the rapid disappearance of large metastatic masses after external irradiation. It is interesting to note that both surgical and roentgen treatment are far more successful in cases of dysgerminoma of the ovary than in cases of testicular tumor of an identical histologic composition.

In cases in which complete removal of the tumor cannot be accomplished, irradiation is the only effective method of treatment. Irradiation for recurrences in the lymph nodes resulted in ultimate cure in 3 cases in the present series. In 1 of these (case 3) there was a

recurrence in the retroperitoneal nodes one and one-half years after the primary operation. The patient received repeated courses of high voltage roentgen therapy during five years and at the time of writing has remained well for twelve years after the operation. In the second

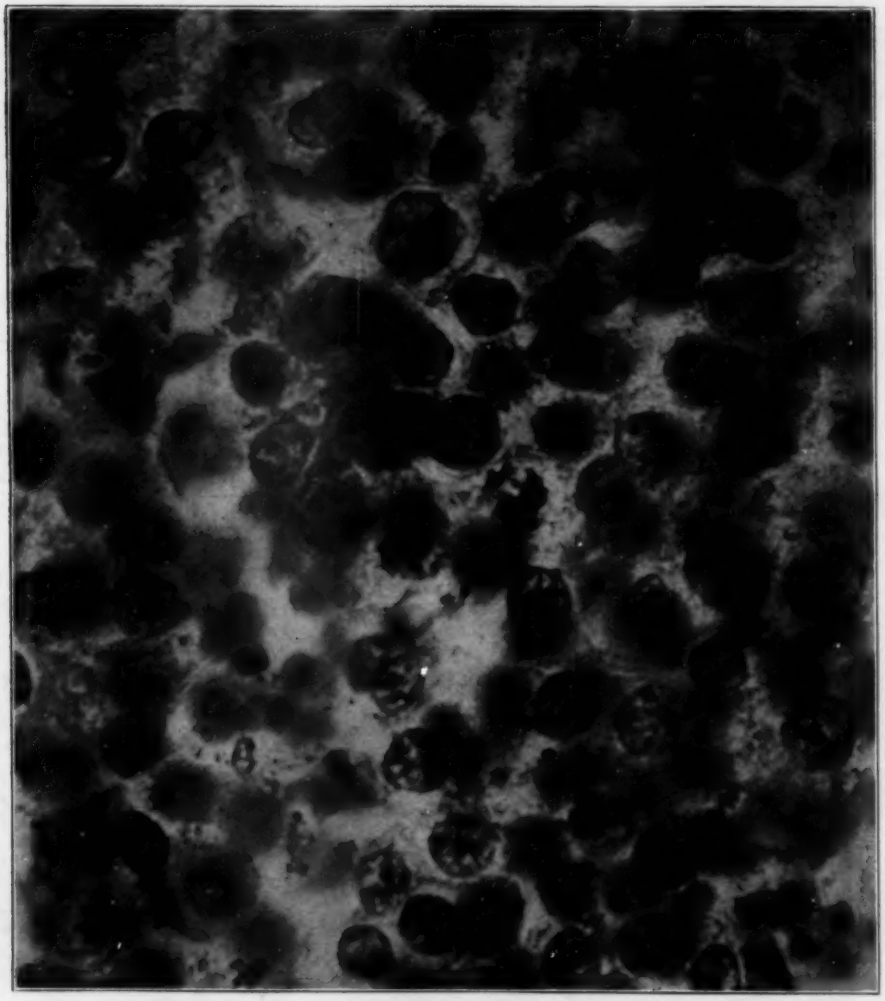

Fig. 4 (case 1).—High power photomicrograph showing the apparently malignant histologic composition of the tumor, with numerous mitotic figures. This patient with dysgerminoma remained well twenty years after the operation. Compare with figure 5.

case (case 5) the condition was treated by implantation of radon seeds into a recurrent tumor mass in the right lumbar region. The patient has remained well more than five years. In a third case (case 12)

the patient's condition was much improved after high voltage roentgen therapy. She was apparently free of tumor three years later, at which time death occurred from pneumonia.

HISTOGENESIS

The histogenesis of dysgerminoma of the ovary is not yet established. The most widely accepted theory at present is that of Meyer,

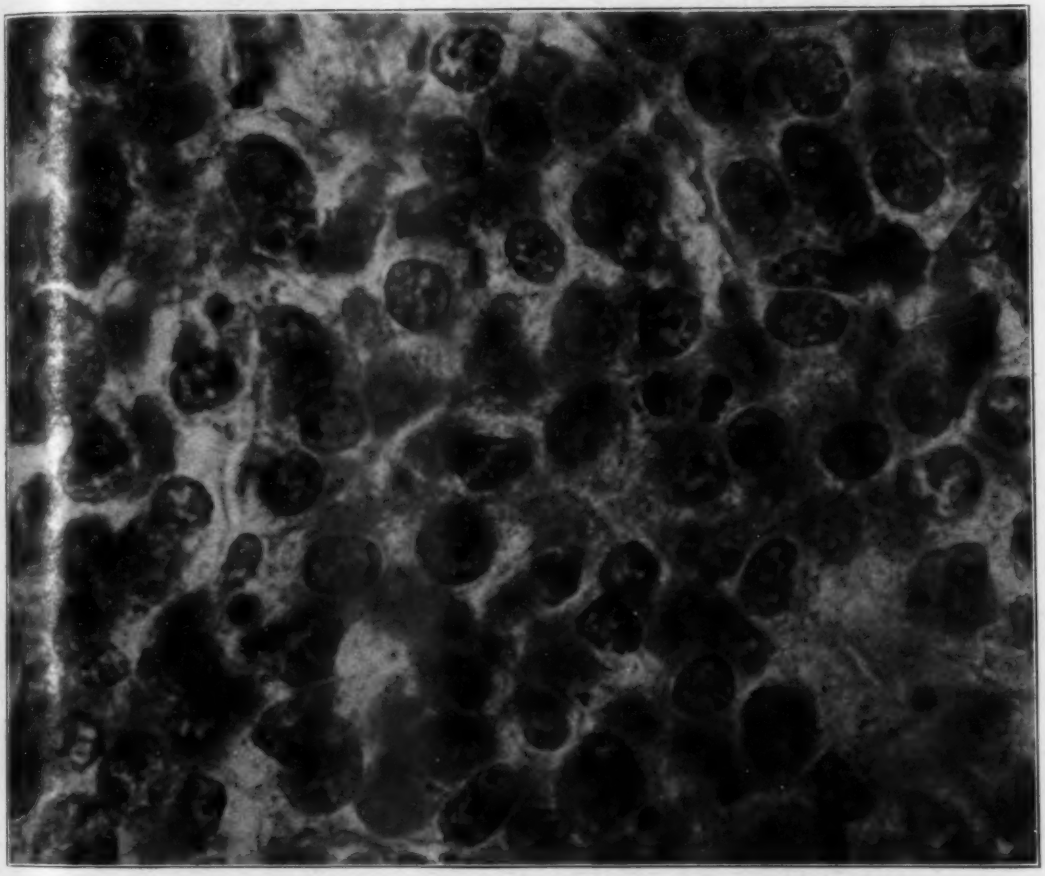

Fig. 5 (case 2).—High power photomicrograph of an ovarian dysgerminoma similar in histologic composition to that in case 2 (fig. 4). This tumor infiltrated the bladder and the retroperitoneal lymph nodes. The patient died eleven months after the operation.

who concluded that the tumor cells are derived from indifferent germ cells of the genital ridge. He stated the belief that such an origin from indifferent germ cells which retain the power to produce both the male and the female gonads accounted for the common occurrence of such tumors in hermaphrodites. It would also account for the occur-

rence of dysgerminoma tissue in cases of teratoma of the ovary and chorioepithelioma of the testis, reported in the literature. Meyer stated that the occurrence of dysgerminoma in otherwise normal women is against the view of Chenot, who concluded that the tumor is derived from the cells of the testicular anlage in the woman. However, since each female gonad passes through a stage corresponding to that of the male, thus making every female temporarily a potential hermaphrodite, it is impossible to say that somewhere in the ovaries of apparently normal women there is not a small focus of male anlage remaining, which gives origin to dysgerminoma. Moreover, the fact that the tumor is about three times as common in the testis as in the ovary seems to favor such an origin.

One observation bearing on the histogenesis of dysgerminoma is its predilection for the right ovary. In 48 per cent, or 35, of the cases reviewed the tumor occurred in the right ovary, while in 26 per cent, or 18, the condition was bilateral. Only 26 per cent of the tumors arose from the left ovary. Of these, 2 occurred in patients who had no right gonad (table 6). This is significant when viewed embryologically, for

TABLE 6.—*Location of Tumor*

	Location		
	Right Ovary	Left Ovary	Bilateral
Cases (Surg. path. lab.)	11	4	2
Cases (literature)	35 (48%)	19 (26%)	19 (26%)

the right ovary develops more slowly and to a lesser degree than does the left ovary. Also, from the standpoint of comparative anatomy it is known that in birds the right ovary remains undeveloped throughout life. Thus, if undifferentiated tissue remains behind, the probability of its occurrence in the right ovary is greater than in the left, and if the tumor is derived from such embryonic tissue, which seems to be the case, it is not surprising that it occurs more frequently in the right ovary. The following cases are from the records of the laboratory of surgical pathology.

REPORT OF CASES

CASE 1 (Dr. J. King B. E. Seegar, Baltimore).—L. S., a girl aged 14, was admitted to the hospital because of violent pain in the left side of the abdomen, accompanied with nausea and vomiting of one day's duration. The menstrual periods had begun at the age of 13 and were still irregular. The last period occurred two months previous to the onset of the present illness. Examination of the abdomen showed rigidity in the lower left quadrant, with marked tenderness. Pelvic examination showed normal external genitalia. The uterus was small and was pressed backward. To the left there was a large irregular mass occupying the lower part of the abdomen, anterior to the uterus. A clinical diagnosis of ovarian cyst with twisted pedicle, probably a dermoid, was made, and operation was performed immediately. The tumor involved the left ovary and had a twisted

pedicle. It was completely free, with no points of adhesion. The tumor and the left tube and ovary were removed. The other pelvic organs were normal. On gross examination the tumor was seen to be the size of a child's head. It was solid and grayish and had an elastic feel. The impression from the gross specimen was that the tumor was a sarcoma. The microscopic picture was typical of dysgerminoma. A follow-up report in November 1936, twenty years after the operation, stated that the patient is well and has five children.

CASE 2 (Dr. J. King B. E. Seegar, Baltimore).—E. S., a woman aged 19, entered the hospital with the complaint that she had never menstruated. There had been frequent voiding of urine and nocturia of increasing severity during the past year. Physical examination revealed a poorly nourished woman with a hard, nodular mass palpable in the abdomen, filling both lower quadrants and reaching to the renal area on the right. The pelvic examination showed normal external genitalia and a hard nodular mass filling the entire cul-de-sac, pushing the small uterus far to the right. The rectal examination showed enlarged retroperitoneal glands. At operation the mass, which arose from the right ovary, completely filled the pelvis and infiltrated the bladder. The iliac and retroperitoneal glands were involved. There were a large tumor about the right kidney and questionable infiltration of the rectum. The uterus was infantile, and the left ovary was only 1 cm. in diameter. The large tumor was extirpated; bilateral salpingo-oophorectomy and hysterectomy were performed. Grossly the tumor mass was seen to be about 15 cm. in diameter and was firm. On section the tissue was coarsely granular, with widely separated fibrous septums. The microscopic diagnosis at the time was carcinoma of the ovary. Reclassification of the tumor showed it to be a dysgerminoma (fig. 6). The patient died eleven months after the operation.

CASE 3 (Dr. Joseph C. Bloodgood, Baltimore).—S. E., a white woman aged 26, married, had one child aged 1 year. The menstrual history was normal. She complained of vague abdominal distress, and on physical examination a large, firm tumor in the lower part of the abdomen was found, which apparently arose from the left ovary. At operation a large, freely movable tumor of the left ovary was removed; the right ovary was normal. The diagnosis was large round cell sarcoma, and the patient was given roentgen treatments in November 1923 and in January 1924. On reclassification this tumor was found to be a dysgerminoma (fig. 7). In May 1925 there was a recurrence. A second laparotomy revealed involvement of the retroperitoneal glands by tumor tissue microscopically similar to that found at the time of the first operation. Thereafter the patient received irradiation treatments every six months until 1930. In June 1930 the mass had completely disappeared, and the patient was asymptomatic. The patient was reported well in June 1935, twelve years after the date of the first operation.

Although at operation this tumor was apparently benign, as judged by complete mobility and absence of infiltration, there was widespread recurrence. The response of the recurring tumor to irradiation suggests that frankly malignant tumors, such as that in case 2, should also respond to such therapy.

CASE 4 (Dr. J. Wainwright, Scranton, Pa.).—M. S., a girl aged 13, complained of pain in the lower part of the abdomen one week prior to admission. The menstrual periods had begun at the age of 12 and had been regular. On physical examination a large tumor was found in the lower part of the abdomen, and an exploratory laparotomy revealed bilateral ovarian tumor. Bilateral salpingo-oophorectomy and hysterectomy were performed. On gross examination the tumors were seen to be firm, solid and whitish and to have irregular surfaces. The microscopic diagnosis was bilateral dysgerminoma (fig. 8). The patient was

20 years of age when last heard from, Dec. 29, 1936, seven years and ten months after the operation. She was in excellent health, and there was no evidence of metastasis.

CASE 5 (Dr. V. Norwood, Baltimore).—B. P., a man aged 39, a pseudohermaphrodite, complained of nausea, vomiting and pain in the right lower quadrant

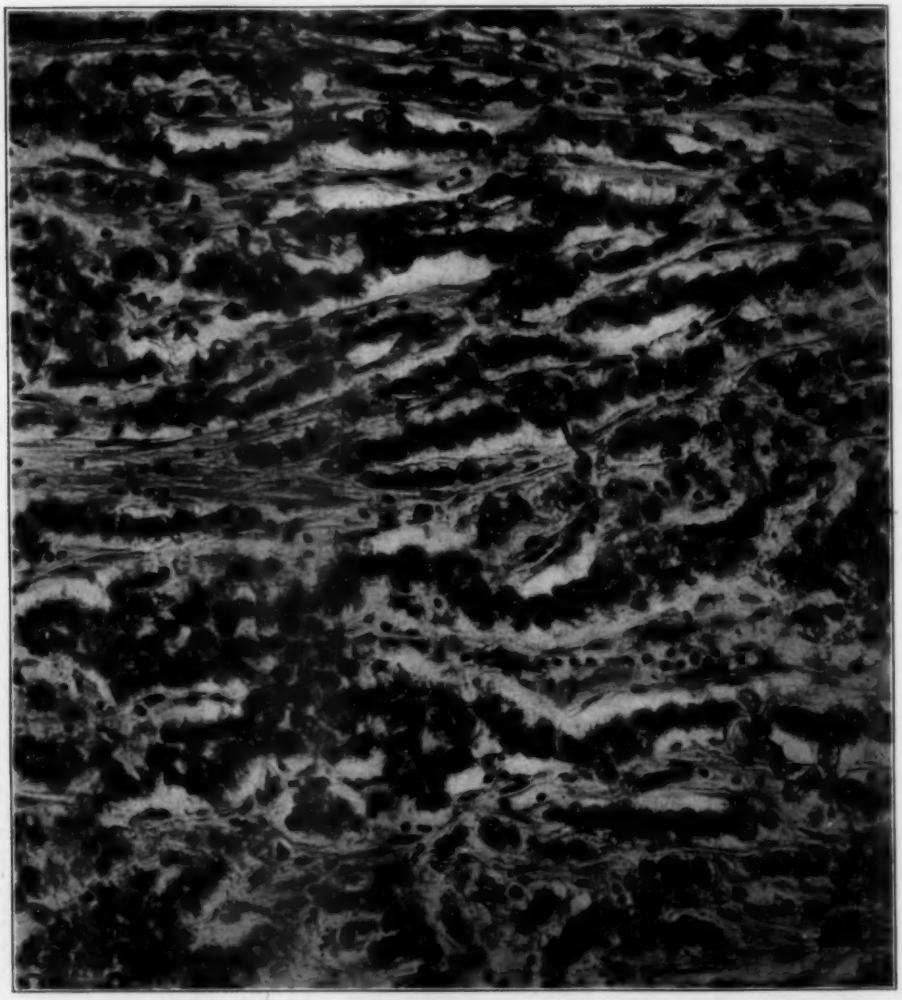

Fig. 6 (case 2).—Photomicrograph of a dysgerminoma which was first diagnosed as carcinoma.

of the abdomen. Physical examination showed a well developed man 6 feet (183 cm.) tall, broad shouldered, with a heavy voice, female distribution of hair, a small penis, an undescended testicle and a hernia in the left side of the scrotum. The patient was married; his marital relations were normal, but his wife had never become pregnant. An operation revealed undescended testicles with a tumor of the right testicle, fallopian tubes and a uterus but no ovarian tissue. The

tumor, both testicles, the tubes and the uterus were removed. The patient left the hospital in good condition but never regained his health completely. He returned to the hospital six months later with identical complaints. Physical examination at this time revealed a firm, freely movable, tender mass in the right renal region. After cystoscopic examination a right posterior lumbar incision was made, and the kidney was exposed; it was found to be embedded in a large mass of tumor tissue, and radon seeds were implanted. Seven emanation seeds containing 3 milli-

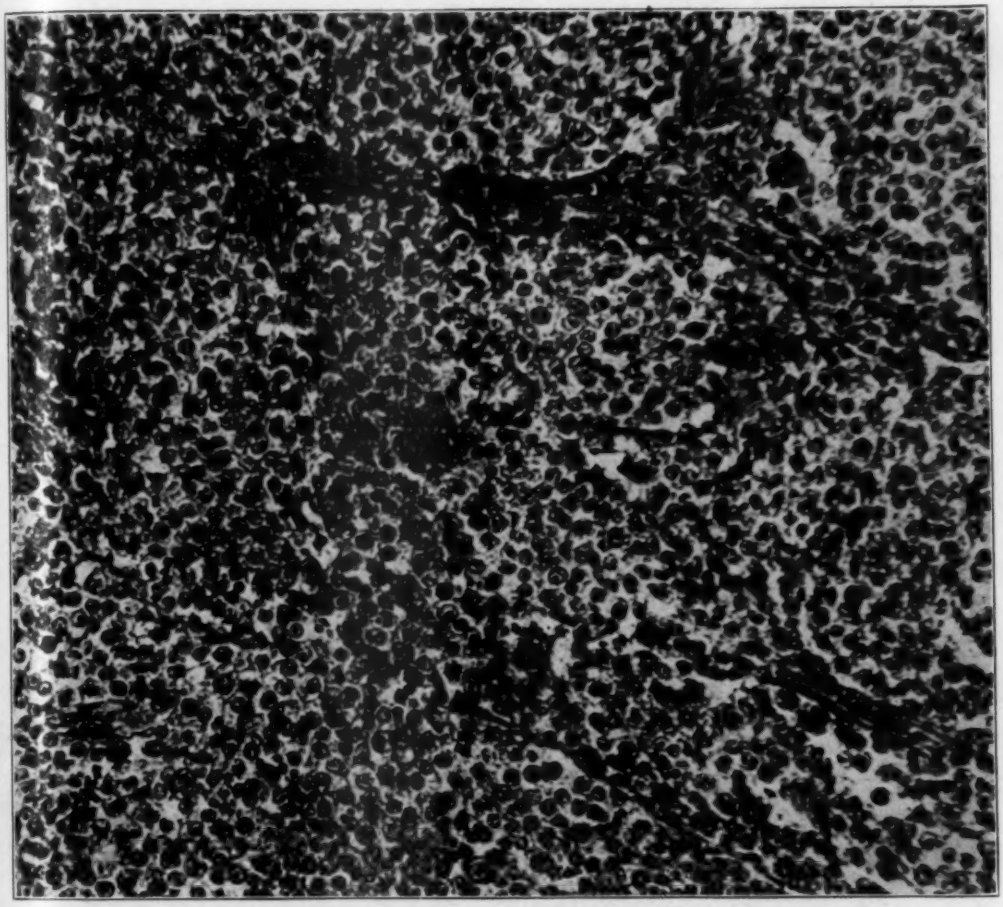

Fig. 7 (case 3).—Photomicrograph of a dysgerminoma which occurred in a unipara aged 26.

curies each were implanted, making a total dose of 2,771 milligram hours. Two months later this dose was repeated. The microscopic diagnosis was dysgerminoma (fig. 9). Five years after the original operation (Feb. 22, 1937) the patient was well, weighing 230 pounds (104 Kg.) and doing manual labor. This case illustrates the more advanced age at which the tumors occur in men and in pseudohermaphrodites. This is the second case with widespread recurrence in the lymph nodes in which the condition responded to irradiation.

Case 6 (Dr. V. Norwood, Baltimore).—P. P., a woman aged 26, married, complained of dizziness, nausea and a heavy feeling in the head for three weeks. The menstrual periods began at the age of 14; they were regular, of three days' duration and accompanied by profuse bleeding and by dysmenorrhea. There was no record as to whether the patient had ever been pregnant. Physical examination revealed a well developed, well nourished woman. Routine pelvic examination showed a small tumor of the left ovary. At a second examination, six months later, it was noted that the tumor had increased threefold, and operation

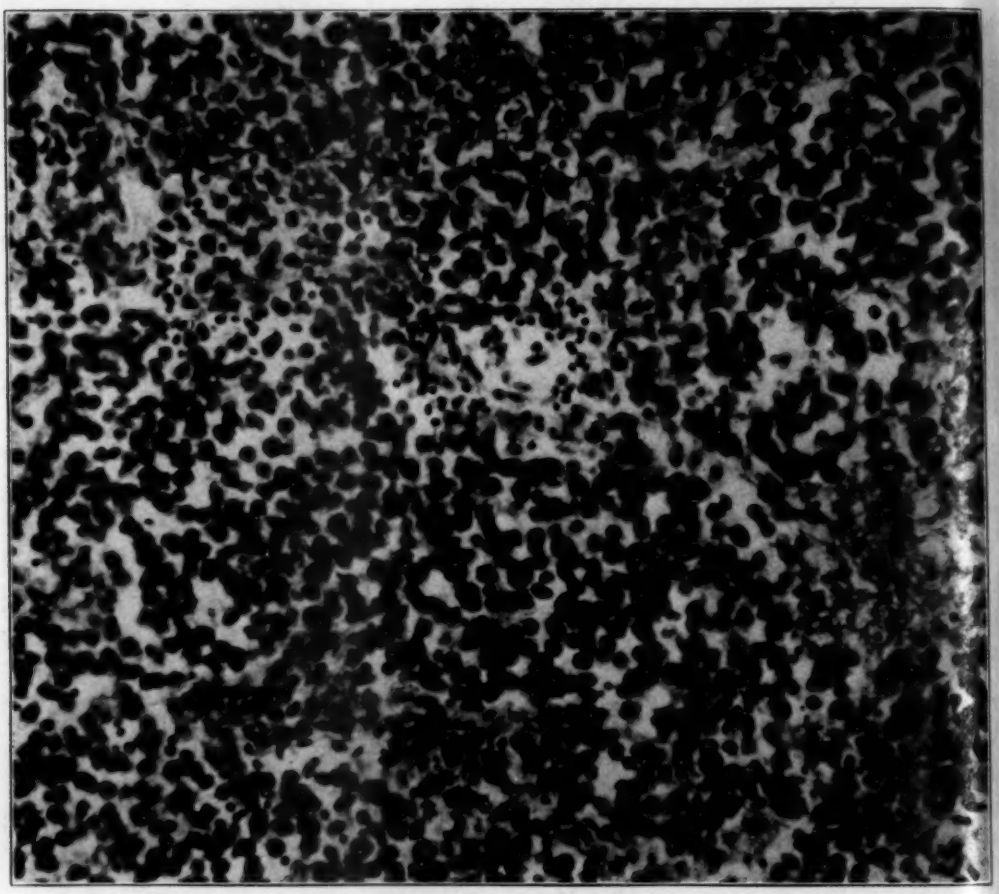

Fig. 8 (case 4).—Photomicrograph of a dysgerminoma which occurred in a girl aged 13. The lesion was bilateral.

was advised. At operation a large, freely movable mass was found occupying the region of the left ovary, and a mass the size of an orange was observed in the left tube. The right ovary was normal. A salpingo-oophorectomy was performed on the left side, and the patient was well six years later (1930) with no evidence of recurrence. Microscopic examination of the tumor showed a typical dysgerminoma. It is of interest to note that this tumor was practically asymptomatic.

CASE 7 (Dr. Louisa Keasbey, Lancaster, Pa.).—A woman aged 38 had normal menstrual periods and had had ten normal pregnancies. In a routine pelvic examination at the time of a thyroidectomy a mass was discovered, which grew rapidly for six months; at the end of this time an operation was advised. Exploratory laparotomy was performed, and a solid circumscribed tumor of the ovary was excised; the tumor weighed 2,340 Gm. After the operation the patient was given massive doses of roentgen therapy. The microscopic diagnosis was dysgerminoma. Two years after the abdominal operation she was reported well.

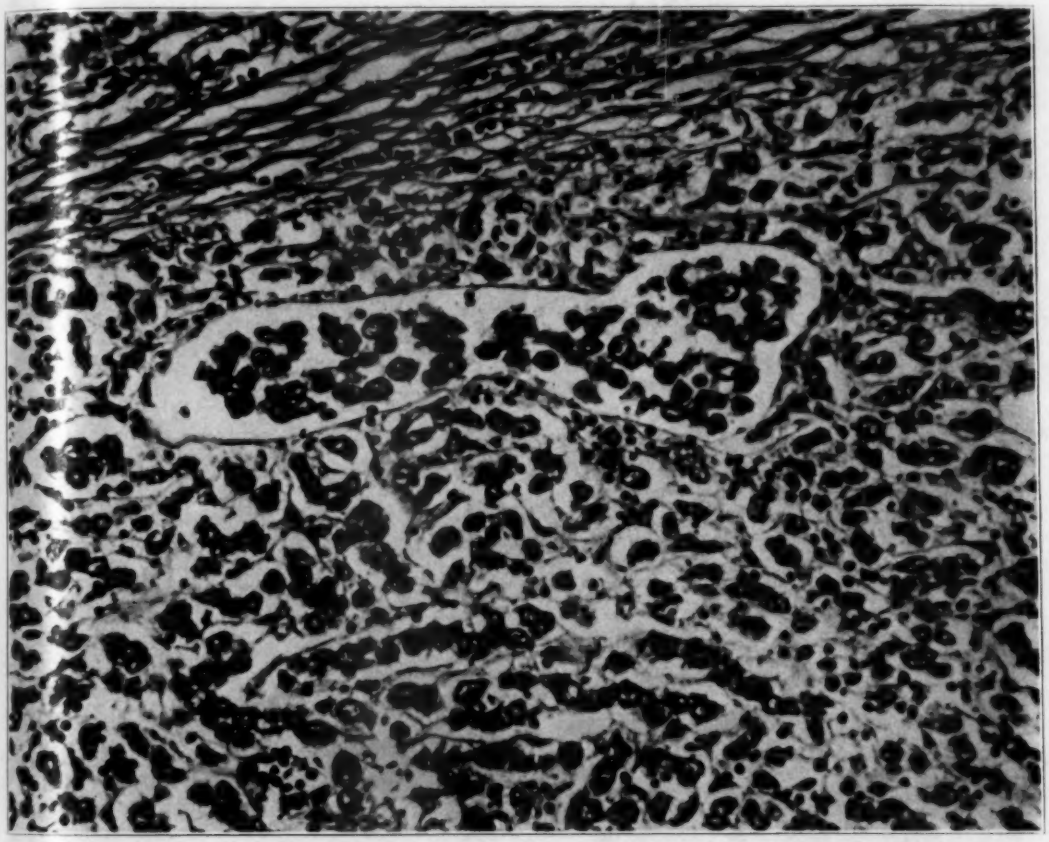

Fig. 9 (case 5).—Photomicrograph of a dysgerminoma which occurred in a male pseudohermaphrodite.

CASE 8 (Dr. George R. Moffitt, Harrisburg, Pa.).—A girl aged 12 had an abdominal swelling of six months' duration. No menstrual history was given. On physical examination the child appeared emaciated. The ankles were edematous, and there was abdomnial swelling with signs of intra-abdominal fluid. No tumor was palpable. A laparotomy was performed, and a large tumor arising from the right ovary was removed. There was marked ascites. The child was reported well four months after the operation. Although ascites is generally considered a bad prognostic sign, in this case the tumor was well circumscribed and easily removed. The histologic character of this tumor is shown in figure 10.

Case 9 (Dr. E. D. Funk, Reading, Pa.).—L. B., a woman aged 18, began to menstruate at the age of 12. The periods were regular; there was a moderate amount of dysmenorrhea. She had noticed a painless progressive swelling of the abdomen for the past six months. A constant, sticking pain in the right side had been present for one week. Physical examination showed a distended abdomen and a mass extending from the pelvis to the umbilicus. The mass was hard, nodular, slightly movable and dull to percussion; no evidence of fluid was observed. There was also some tenderness in the right flank. The external genitalia were

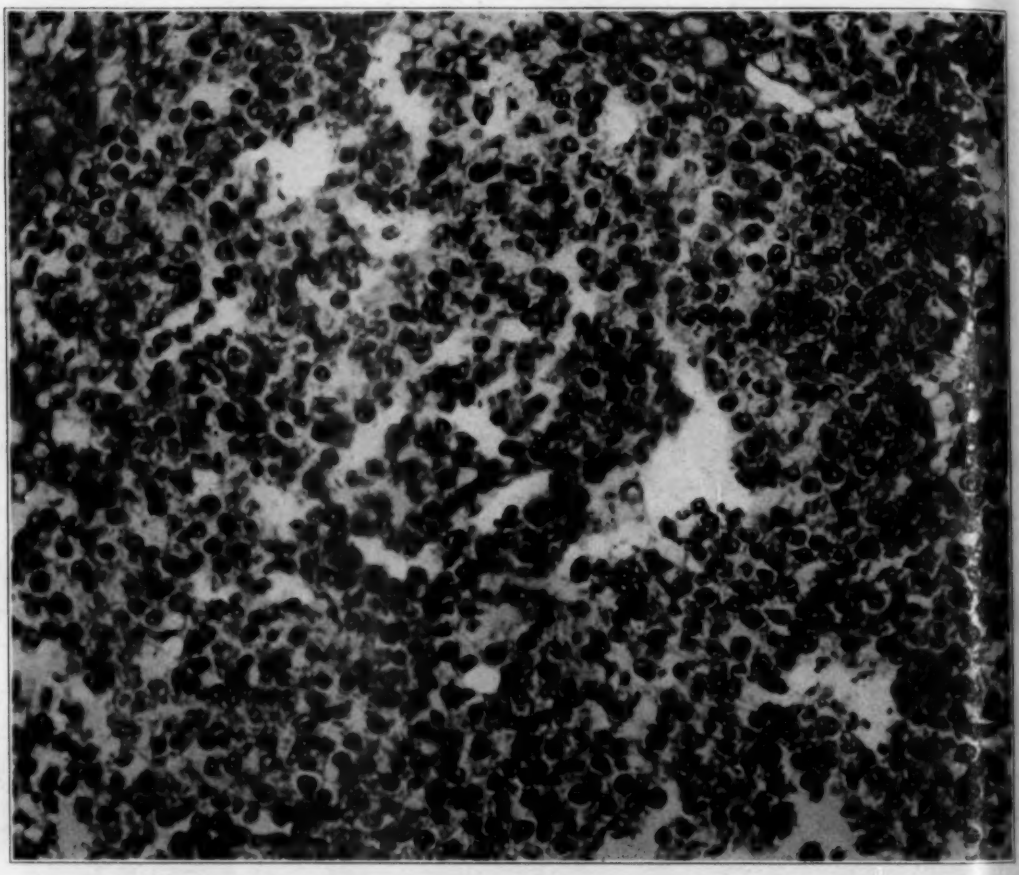

Fig. 10 (case 8).—Photomicrograph of an ovarian tumor which occurred in a girl aged 12.

normal. An exploratory laparotomy revealed a tumor of the right ovary, measuring 4 by 13 by 11.5 cm. and weighing 2,010 Gm. A salpingo-oophorectomy on the right side was performed. The gross specimen was smooth, bosselated and pinkish white. The cut surface was smooth, firm and grayish. There were no cystic or hemorrhagic areas. The microscopic diagnosis was dysgerminoma of the right ovary. Four months after the operation the patient was reported well with no evidence of recurrence (January 1937).

Case 10 (Dr. G. W. Ramsay, Washington, Pa.).—A woman aged 28, married, began to menstruate at the age of 14. The menses were scanty and irregular;

six years before the present illness they ceased entirely. There were no pregnancies. For two years the patient had complained of a painless enlargement of the abdomen, which had become more marked two months prior to hospitalization. This was accompanied by pain in the sides and in the back. Examination revealed small but well formed breasts. The external genitalia were normal. An operation was performed, and a well encapsulated tumor of the right ovary was removed. The patient died four days after the operation. On gross examination the tumor was irregular and coarsely nodular. It measured 18 by 15 by 8 cm.

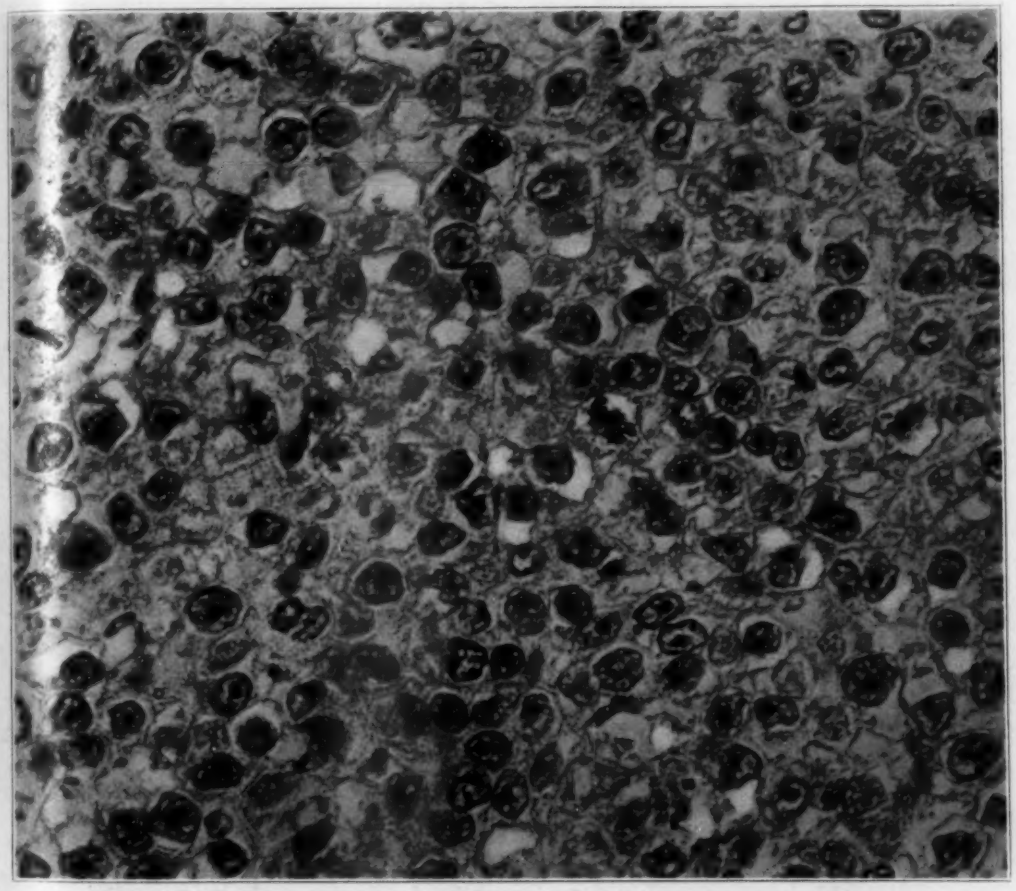

Fig. 11 (case 10).—High power photomicrograph showing the character of the individual dysgerminoma cells. There are frequent mitotic figures. The patient died four days after the operation.

and weighed 1,300 Gm. The cut surface was grayish white and finely granular, with some areas of necrosis. The microscopic diagnosis was dysgerminoma (fig. 11).

Case 11 (Dr. H. C. Lennon, Philadelphia).—M. D., a white woman aged 22, was first seen because of active pulmonary tuberculosis. The menstrual periods had begun at the age of 14 and had always been regular. She was unmarried and had had no pregnancies.

Soon after coming under observation the patient died of advanced pulmonary tuberculosis. At autopsy the right ovary was found to be symmetrically enlarged, measuring 4.5 cm. in diameter. On section a firm, homogeneous, pale encapsulated mass measuring 3.5 cm. in diameter was found embedded in the central portion of the ovary. On microscopic section this nodule showed the typical picture of dysgerminoma (fig. 12).

Clinically the case is interesting in view of the absence of symptoms and the association with tuberculosis. There are cases reported in the literature in which

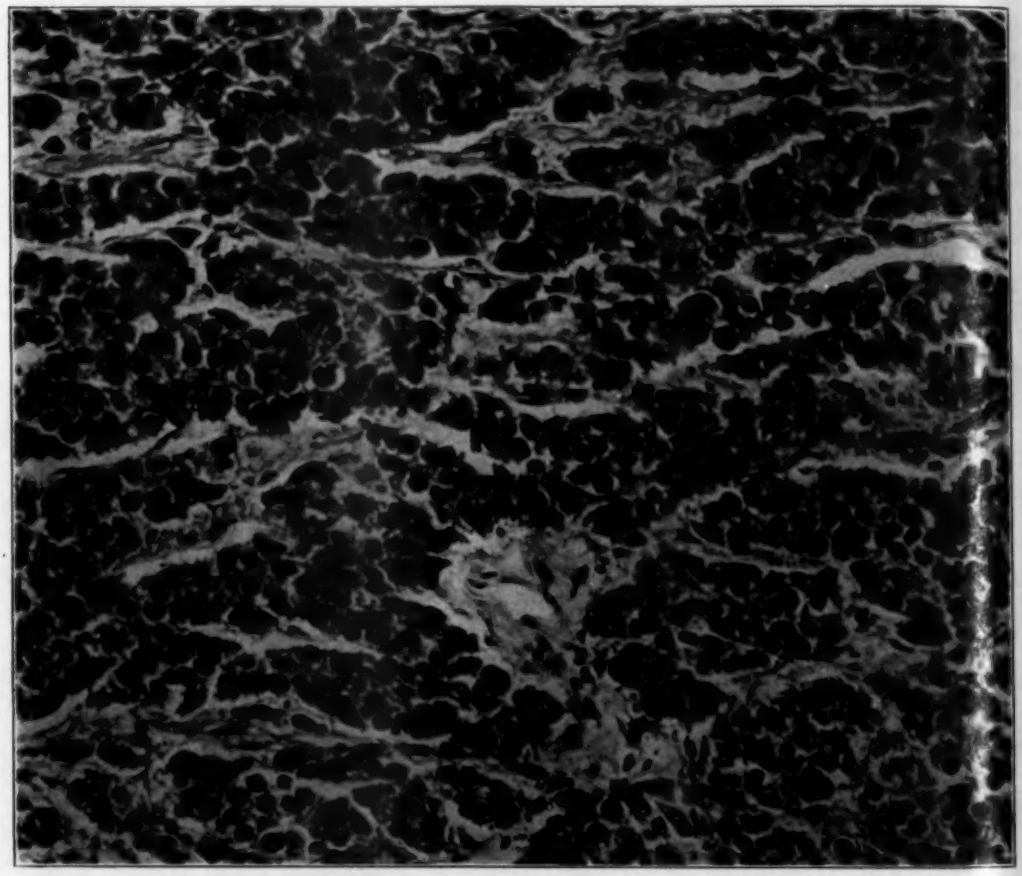

Fig. 12 (case 11).—The photomicrograph of this tumor shows a striking similarity to the medullary cords seen in the developing gonad.

this type of tumor was associated with tuberculosis, and Schiller laid great emphasis on this fact and on the occurrence of giant cells in the tumor.

The small size of the tumor indicates an early lesion. Its location in the hilus of the ovary suggests origin from an embryonal rest, either from the medullary cords or from the indifferent germinal cells of the ovary.

Case 12 (Dr. E. L. Armstrong, Erie, Pa.).—M. C., a woman aged 30, was admitted to the hospital because of nausea and vomiting associated with tenderness in the lower left quadrant of the abdomen. These symptoms had appeared one

year previously, when the patient fell and injured her left side, and had been gradually increasing in severity. There were loss of weight, anorexia and lassitude.

The patient was found to be a pseudohermaphrodite. There was a heavy beard, requiring daily shaving, and a heavy growth of hair covered the extremities. The voice was deep. The skeletal and muscular development was masculine, and the breasts were flat. Examination of the genitalia revealed excessive pubic hair with feminine distribution, a hypertrophied clitoris and perineal hypospadias with the posterior commissure intact. There was no evidence of labial testes. There was a rudimentary vagina, which admitted one finger, and a small cervix was observed, flush with the vaginal mucosa. On rectal examination a firm mass could be felt occupying the left adnexal region and extending into the abdomen.

At operation a spherical tumor 4 cm. in diameter was found lying in the left broad ligament, adherent to the sigmoid flexure of the colon and to the rectum. The tumor was shelled out easily by blunt dissection; there was no pedicle and no attachment to the ovaries, both of which were present. The uterus was infantile. The microscopic diagnosis was dysgerminoma (fig. 13).

The patient was discharged in good condition. However, she was readmitted four months later, with a recurrence of the nausea, vomiting and abdominal discomfort. Examination at this time revealed a small, firm mass in the left lower quadrant of the abdomen, suggesting a recurrence of the tumor. It was also noted at this examination that she had lost the male secondary sexual characteristics to a great extent. As the patient refused to undergo a second operation she was given roentgen therapy. The result was regression of the abdominal mass and complete alleviation of the symptoms.

Three years later she was admitted to the hospital again, this time with lobar pneumonia of the right lung which proved fatal in six days. On this admission it was stated that she had been well during the three year interval, and on physical examination the female sexual characteristics predominated. There was no evidence of a recurrence of the abdominal growth.

In this case there was regression of the male sexual characteristics in a pseudohermaphrodite following extirpation of a dysgerminoma. Such an occurrence has never been reported in the literature to my knowledge, and in view of my conception of the dysgerminoma as a nonsecretory tumor, it would seem that the phenomena in this case were due to coincidence rather than an effect of the tumor.

Here again there was apparently a remarkable response of the recurring tumor to roentgen therapy.

Case 13 (Dr. J. J. Shank, Waynesboro, Pa.).—O. S., a girl aged 12, entered the hospital complaining of progressive enlargement of the abdomen. On physical examination a large mass was palpable, filling the entire right lower quadrant of the abdomen and extending into the right upper quadrant. A tentative diagnosis of renal tumor was made preoperatively. At operation a large pedunculated tumor was found arising in the right broad ligament. It completely filled the pelvis, and the upper pole was free in the abdominal cavity. There were extensive adhesions to the peritoneum, the colon, the omentum and the small intestine. The tumor and the appendix were removed.

The tumor weighed 1,293 Gm. and was surrounded by a dense fibrous capsule. Microscopically the tumor showed the characteristics of a dysgerminoma.

The patient was discharged in good condition, and when last heard from, seven and one-half years after the operation, she was in excellent health, with no evidence of recurrence or metastases.

Case 14 (Dr. Herman H. Van Horn, Harrisburg, Pa.).—M. S., a girl aged 13, entered the hospital complaining of pain in the right lower quadrant of the abdomen and also of nausea and vomiting of three days' duration. She had had recurrent

attacks of pain in the lower part of the abdomen since the age of 6 years. Physical examination revealed a mass the size of a grapefruit in the midline, arising in the pelvis and extending almost to the umbilicus. This mass was dull to percussion, freely movable and not apparently tender. At operation a solid tumor was found, arising in the right broad ligament and replacing the right ovary. The tumor and the right fallopian tube were removed, together with the appendix. The tumor measured 14 by 9 by 9 cm. and weighed 500 Gm. It was completely encapsulated and solid except for one small central cavity containing blood. Micro-

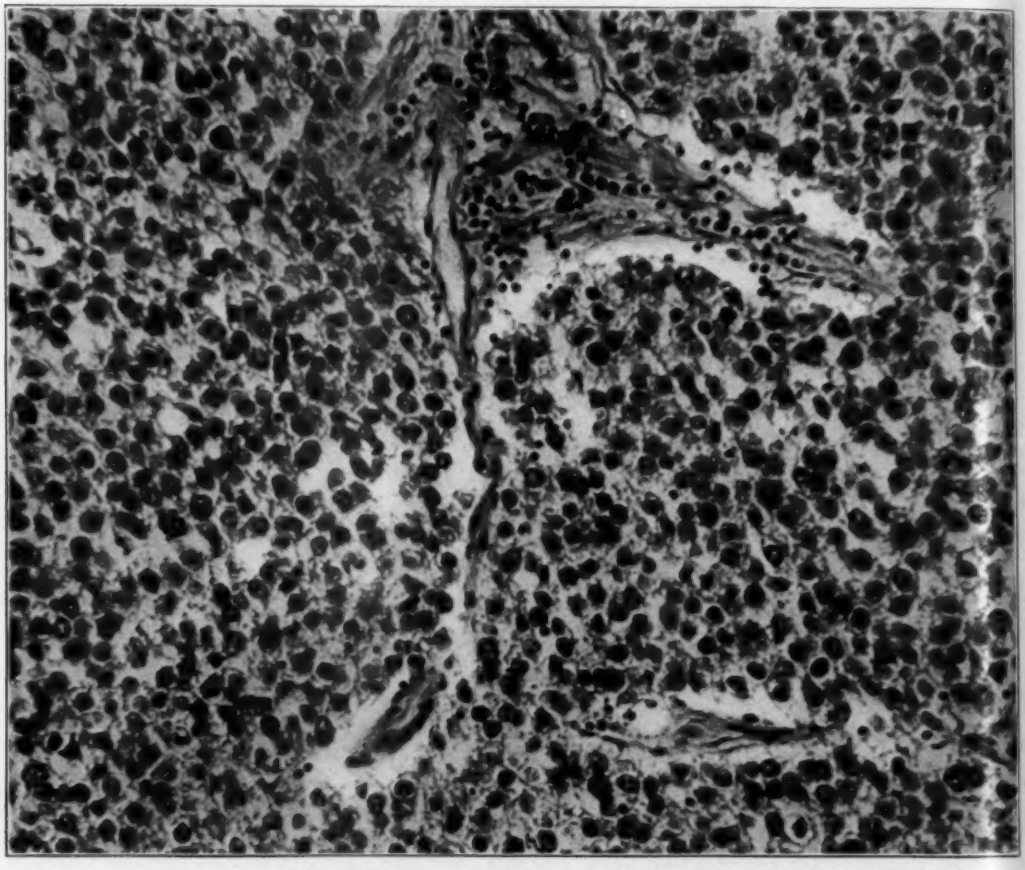

Fig. 13 (case 12).—Photomicrograph of a dysgerminoma which occurred in a female pseudohermaphrodite.

scopic examination revealed a dysgerminoma. The patient was reported well with no evidence of recurrence or metastasis two years and ten months after the operation. The menstrual periods were normal.

Case 15 (Dr. Helen Ingleby, Philadelphia).—A woman aged 34 noticed increasing abdominal enlargement during a period of six months. The menstrual history was entirely normal. She had had one full term spontaneous delivery fourteen years prior to the present illness. At operation she was found to have a tumor of the right ovary, measuring 20 by 16 by 9 cm., with an irregular

nodular surface. On section it was found to be solid throughout; the cut surface was pale and firm and was divided by dense fibrous septums. Microscopic examination showed typical dysgerminoma.

CASE 16 (Dr. Phillip Jaisohn, Media, Pa.).—R. N., a white woman aged 22, was admitted to the hospital complaining of pain in the lower part of the abdomen, present for one week and of an abdominal mass which she had first noticed six months previously. At operation a tumor was found arising from the left ovary. This tumor was encapsulated. It measured 13 by 9 by 5 cm. The smooth, white glistening surface was continuous with the serosa of the ovary, which was located on the anterior superior aspect of the tumor mass. The ovary was somewhat enlarged and contained a serous cyst. The cut surface of the tumor showed it to be compact, with dense areas of stroma. On microscopic examination the tumor proved to be a dysgerminoma.

CASE 17 (Dr. Oliver Lohr, New York).—A white woman aged 31 came to the hospital complaining of a hard mass in the abdomen. No accurate menstrual or obstetric history was available. Physical examination revealed a well developed normal woman with no evidence of pseudohermaphroditism. On abdominal examination multiple hard, nodular masses could be felt in both lower quadrants of the abdomen. On pelvic examination the uterus was found to be irregularly enlarged, and firm, nodular masses were palpated in both adnexal regions. The Aschheim-Zondek test gave a negative reaction.

At operation tumors were found replacing both ovaries and involving the retroperitoneal glands. The uterus was also invaded by the tumor tissue and contained, in addition, a small fibroid. The patient survived the operation but died within the month. Autopsy confirmed the operative findings

The pathologic diagnosis was bilateral dysgerminoma of the ovaries with invasion of the pelvis and uterus.

CASE 18 (Dr. F. P. McNamara, Dubuque, Iowa).—A girl aged 14 consulted a physician because of abdominal swelling and cramplike pain in the region of the umbilicus. The menses had been regular and normal. Four months prior to the onset of the present illness she had begun to have severe dysmenorrhea, necessitating two days' rest in bed during each period. There had been loss of weight.

Physical examination revealed a normally developed girl with an abdominal mass arising in the pelvis and reaching 3 fingerbreadths above the umbilicus; it was approximately 20 cm. in diameter, nodular, hard and slightly movable. Rectal examination showed this mass to arise apparently from the left ovary. It completely filled the pelvis. Neither the liver nor the spleen was palpable. A tentative diagnosis of ovarian tumor was made.

At operation a large, solid nodular tumor of the left ovary was found. The right ovary was cystic, and the spleen, the pancreas and the left kidney were enlarged and nodular. The ovarian mass only was removed. The pathologic diagnosis was dysgerminoma of the left ovary with generalized visceral metastases.

The immediate postoperative course was uneventful. The patient was next seen two years later; there were nodular masses throughout the abdomen. She was extremely cachectic. Roentgen therapy was instituted, and the tumor masses promptly receded. She gained weight, lost her haggard appearance and for a year and a half seemed almost like a normal girl of 16. The neoplasm then reappeared, and this time it did not respond to roentgen therapy. She failed rapidly and died four years after the onset of the first symptoms.

CASE 19 (Dr. Vernon Norwood, Baltimore).—A woman aged 28 was admitted to the hospital after an attack of pain in the lower part of the abdomen and nausea of twenty-four hours' duration. The menstrual periods had been regular.

Examination revealed a protuberant abdomen with a firm mass on the right side, extending from the pelvis to the umbilicus. The clinical impression was right ovarian cyst with torsion of the pedicle. Laparotomy was performed. A tumor the size of a man's head was found in the region of the right ovary. The peritoneal cavity was studded with metastases, and a secondary growth the size of an adult fist was found in the omentum. The ovarian tumor only was removed. Ascites developed after the operation, and the patient died one month after removal of the ovarian tumor. A description of the pathologic specimen is not available.

The sections of the tumor were unusual (fig. 3). They showed typical dysgerminoma tissue associated with a vascular malignant growth containing many large spindle cells and epithelial cells, suggesting chorionic tissue. A few giant cells were scattered through this vascular tissue. The microscopic diagnosis was dysgerminoma associated with atypical chorionic tissue or sarcoma of the ovarian stroma.

SUMMARY

The data on 79 cases of dysgerminoma reviewed in the literature are summarized, together with those on a series of 19 cases recorded in the laboratory of surgical pathology. Dysgerminoma is a relatively rare tumor, the incidence being under 3 per cent of all malignant ovarian neoplasms. It occurs in young persons, usually in those under 30 years of age, 48 per cent of the growths being in the right ovary and 26 per cent bilateral. Occasionally the tumor is associated with sexual underdevelopment or maldevelopment. Rapid growth of the neoplasm results in an abdominal mass which on pelvic examination is found to be an elastic, nodular tumor arising from the adnexal region; in the benign form it is well circumscribed and freely movable; in the more malignant types, infiltrative, with extensive metastatic involvement of the retroperitoneal glands, the peritoneum, the omentum, the bladder and the rectum. Metastases to distant organs are extremely rare, and metastasis to the lungs has not been reported. Microscopically, dysgerminoma is characterized by large, discrete germinal cells of a caviar-like appearance and by abundant lymphoid stroma. Dysgerminoma may be associated with other forms of ovarian tumor, such as teratoma or chorioepithelioma. I have found it impossible to differentiate the benign and the malignant form histologically. However, from the history and the findings at operation it is sometimes possible to prognosticate correctly. These tumors have a mortality between 35 and 60 per cent, with a slightly higher rate of recurrence and metastasis. These figures are based on follow-up reports found in a series of 50 cases reported in the literature and on the results of treatment in 17 of 19 cases followed in the present series. The treatment of choice is removal of the tumor and the affected tube and ovary only. Recurrences and metastases are best treated by excision and roentgen therapy, although in 1 case the tumor was successfully treated by roentgen therapy alone. In cases in which removal of the mass is impossible the patients should be given the benefit of irradiation therapy.

BIBLIOGRAPHY

Babes, A.: Arch. f. Gynäk. **135**:545, 1929.

Bonnet, P.: Lyon chir. **25**:191, 1928.

Chenot, M.: Contribution à l'étude des épithéliomes primitifs de l'ovaire, Thesis, Paris, no. 129, 1911.

Chevassu, M.: Rev. de chir., Paris **30**:628, 1910; Tumeurs du testicule, Thesis, Paris, no. 193, Paris, G. Steinheil, 1906.

Desmarest and Masson: Bull. et mém. Soc. anat. de Paris **87**:448, 1912.

Döderlein, G.: Zentralbl. f. Gynäk. **60**:1027, 1936.

Du Pont, R., and Simard, L. C.: Bull. et mém. Soc. anat. de Paris **95**:124, 1925; Bull. Soc. d'obst. et de gynéc. **14**:195, 1925.

Dworzak, H.: Arch. f. Gynäk. **151**:281, 1932.

Fauvet, E.: Zentralbl. f. Gynäk. **58**:2162, 1934; **60**:675, 1936.

Ferguson, R. S.: Am. J. Cancer **18**:269, 1933.

Frankl, O.: Zentralbl. f. Gynäk. **60**:1682, 1936.

Gilliard, A.: Strahlentherapie **52**:226, 1935.

Gross, cited by Matsner.

Hajek, O.: Zentralbl. f. Gynäk. **59**:317, 1935.

Hammant, A., and Cornil, L.: Bull. Soc. d'obst. et de gynéc. **14**:606, 1925.

Hartmann; Ménétrier, P., and Isch-Wall, P.: Bull. Assoc. franç. p. l'étude du cancer **11**:319, 1922.

Hoche, J.: Bull. Assoc. franç. p. l'étude du cancer **19**:476, 1930.

Keller, cited by Matsner.

Klaften, E.: Zentralbl. f. Gynäk. **57**:36, 1933; Arch. f. Gynäk. **158**:544, 1934.

Klein, H. O.: Arch. f. Gynäk. **158**:9, 1934.

Laffont and Bonafos: Bull. Soc. d'obst. et de gynéc. **23**:642, 1934.

Lubarsh, cited by Matsner.

Matsner, E. M.: Arch. f. Gynäk. **119**:563, 1923.

Ménétrier, P.; Peyron, A.; Isch-Wall, P., and Lory: Bull. Assoc. franç. p. l'étude du cancer **11**:185, 1922.

Meyer, R.: Arch. f. Gynäk. **109**:212, 1918; **123**:675, 1925; **145**:2, 1931; Zentralbl. f. Gynäk. **49**:1244, 1925; Am. J. Obst. & Gynec. **22**:697, 1931.

Neumann, H. O.: Ztschr. f. Geburtsh. u. Gynäk. **98**:78, 1930; Arch. f. Gynäk. **130**:742, 1927; **131**:477, 1927.

Pick, cited by Matsner.

Reifferscheid, W.: Ztschr. f. Geburtsh. u. Gynäk. **110**:273, 1935.

Rössle: Monatschr. f. Geburtsh. u. Gynäk. **35**:244, 1912.

Schiller, W.: Arch. f. Gynäk. **158**:1, 76 and 89, 1934; J. Obst. & Gynaec. Brit. Emp. **43**:1134, 1936.

Szathmáry, Z.: Arch. f. Gynäk. **153**:333, 1933.

Tietze, K.: Arch. f. Gynäk. **146**:197, 1931.

Wallis, O.: Zentralbl. f. Gynäk. **57**:729, 1933.

Wolfe, S. A., and Kaminester, S.: Am. J. Obst. & Gynec. **29**:71, 1935.

Zacharias, cited by Matsner.

Zimmerman, cited by Matsner.

Zondek, B.: Gonadotropic Hormone in Diagnosis of Chorionepithelioma, J. A. M. A. **108**:607 (Feb. 20) 1937.

Zucker, cited by Matsner.

INFECTIONS OF THE HAND

THREE YEARS' EXPERIENCE IN A CLINIC FOR STUDY OF WHITLOW

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A clinic for the study of whitlow was started at University College Hospital at the end of 1933. The patients seen at the clinic, which is held once a week, are referred from the casualty department because of minor injury of the hand and whitlow, the latter being defined as a focal infection of the hand. The function of the clinic is advisory, treatment remaining in the hands of the casualty officers.

INCIDENCE

In the three years from 1934 to 1936, inclusive, 41,474 patients were seen in the surgical division of the casualty department. Of this number, 388 patients had infection or injury of the hand, that is, such patients account for just under 1 per cent of the patients in the surgical division of the casualty department (table 1). The slight rise in the incidence of such disorders in 1936 is probably due to the greater care now taken to refer the patients to the clinic. The figures given in table 1, showing the number of cases of injury and infection observed

TABLE 1.—*Incidence Among Patients in the Casualty Surgical Department*

Year	No. of Patients	Whitlows and Injuries	Percentage
1934	13,312	118	0.88
1935	13,344	119	0.89
1936	14,818	151	1.02
Total	41,474	388	0.93

at the clinic, do not include all such cases in which treatment was given at the hospital during this period, for the following reasons:

1. After the clinic was started, some time passed before the mechanism of collecting its patients was working efficiently, and some patients missed attendance.

2. Some patients attend for dressings at night, and a few of these are unable to attend the regular sessions of the clinic.

3. Patients with serious symptoms are usually admitted to the wards as soon as they are seen and on discharge may or may not attend the clinic.

From the University College Hospital.

4. Injuries and infections occurring among the members of the nursing staff are not seen at the clinic.

With the exception of the patients among the nursing staff I do not think that many patients have missed attendance at the clinic.

AGE

As may be seen in table 2, in about 60 per cent of cases the injury or infection occurred in the second or the third decade of life, and cases were more or less equally distributed between them.

TABLE 2.—*Distribution According to Age*

Age (Years)	Number of Patients
0-10	24
11-20	128
21-30	104
31-40	51
41-50	50
51-60	21
Over 60	10
Total	388

Youngest 1 year; oldest 75 years.

OCCUPATION

There was a great variety of occupations. Children, including school children, accounted for 18 per cent of the patients, and the majority of the remainder were manual laborers, craftsmen, housewives and domestic servants. There were comparatively few clerical workers.

SEX

The number of male and of female patients affected by casualties is approximately equal, and this was true of the series presented, 195 patients being men and 193 women. Injury occurred nearly twice as frequently in men as in women, and paronchyia, nearly twice as frequently in women as in men. In the former class the distribution is probably due to the nature of the occupation pursued; in the latter, to the practice of manicuring the nails. In all 6 cases of carbuncle of the fingers or the hand the patients were men. This incidence may be associated with the greater hairiness of the male hand. For the other types of infection the incidence was about equal in both sexes, or the number of cases recorded was too small to enable the drawing of any conclusions.

TRAUMA

Of the 388 cases 61 were cases of injury. If this number be subtracted, 327 cases of infection remain, and of these there was a history of injury in 192, or 58.7 per cent. Only those cases in which the

patient could describe the type of injury and the time of its infliction are included in the group in which there was a history of injury, although in many other cases it seemed probable from the appearance of cuts and scratches on the hands that injury had preceded infection. All patients with a history of trauma were asked whether precautions had been taken to prevent infection. Only 3 had received first aid, although it was available to many more. The injuries were in most cases comparatively trivial; they varied in character, injuries due to crushing, to cuts and to pricks being the commonest. A common complication of trivial injury is the entry of a foreign body. If the injury is followed by infection the retention of the foreign body will delay or prevent healing. In 4 cases in the series, a retained foreign body caused prolonged suppuration, and in all 4 cases rapid healing followed its removal. In only 1 of these cases was the presence of a foreign body suspected by the patient. In any case of unexpected delay in healing the possibility of a retained foreign body must be considered.

If the various types of infection are considered, it is seen that there is no significant difference between them in the proportion of cases in which trauma precedes infection. Thus, of the cases of infection of the digital pulp, of paronychia and of subcutaneous abscess and cellulitis of the fingers, trauma occurred in 64, 50 and 65 per cent, respectively. With the other types of whitlow the figures were not large enough to indicate the significance of trauma.

HAND AFFECTED

The right hand was affected in 192 cases, the left in 159 and both hands in 6; for 31 patients there was no note as to which hand was affected. No note was made of the right-handedness or left-handedness of the patients, so it is impossible to estimate the importance of this factor.

FINGERS AFFECTED

Table 3 shows that the index and the middle finger and the thumb were affected most frequently and to an equal extent. The ring finger was involved half as frequently as was any of the first three digits, and the little finger half as frequently as the ring finger. This was true of the series as a whole. It is also true of the individual types of infection, with the exception of paronychia, when the number of cases is sufficiently large to be useful. In this type of whitlow the index, the middle and the ring finger are affected equally commonly, and the thumb twice as commonly as any one of these digits.

TYPES OF WHITLOW

The categories in which the cases of this series have been placed are mostly self explanatory. In order to remove any ambiguity it may be stated:

1. In all cases in which the condition was classified as injury the patient came to the hospital with an injury to the hand and was treated for it. Cases in which the patient was first seen when infection had followed injury are included under the appropriate type of infection.

TABLE 3.—*Fingers Affected*

Type	Thumb	Index	Middle	Ring	Little	Not stated	Total	Remarks
Injury								
(a) By crushing	4	12	12	9	2	1	40	2 patients had 2 fingers affected
(b) Other	8	9	7	3	3	0	30	2 patients had 2 fingers and 1 had 3 fingers affected
Infection of digital pulp								
(a) Uncomplicated; acute.	12	21	14	3	3	2	55	1 patient had 3 fingers affected
(b) With necrosis of terminal phalanx	5	3	3	1	0	0	12	
Paronychia								
(a) Uncomplicated; acute.	30	11	17	13	7	0	87	2 patients had 2 fingers affected
(b) With infection of pulp	3	2	2	1	0	0	8	
(c) Chronic and recurrent	2	1	3	4	1	0	11	
(d) Pus under distal part of nail	3	5	1	2	1	1	13	
Subcutaneous abscess and cellulitis	20	27	21	8	11	2	89	
Carbuncle	1	1	4	0	1	0	7	
Infection of tendon sheath	0	2	4	2	0	0	8	
Suppurative arthritis	2	2	4	0	0	0	8	
Total	99	96	92	46	29	6	368	

2. Cases in which the lesion was classified as subcutaneous abscess and cellulitis of the fingers do not include those of infection of the digital pulp.

3. The group labeled "miscellaneous" includes cases of infections which do not fit into any of the other categories and cases of stiff or painful fingers.

DURATION OF DISABLEMENT

By "duration of disablement" is meant in most cases the period after the onset of the injury or whitlow during which the patient was unable to work.

Among the cases of injury of the fingers by crushing were 5 of compound fracture of the terminal phalanx. In 3 of these the diagnosis was correctly made, and an immediate partial amputation of the terminal phalanx with removal of the nail bed and closure of the wound was

performed. The 3 patients were able to return to work in three weeks. In the other 2 cases the diagnosis was not made until the patient was seen at the whitlow clinic. In 1 the wound healed in four weeks; in the other the fracture became infected, sequestration occurred and the patient was disabled for three months.

TABLE 4.—*Type of Lesion and Duration of Disablement*

Type	Male	Female	Trauma	Total	Duration of Disablement
Injury					
(a) By crushing	20	13	33	33	27 for 1 to 4 weeks 6 for 6 weeks and longer
(b) Other	19	9	28	28	1 not known (ceased attendance) 22 for 1 to 4 weeks 5 for longer than 4 weeks
Total injury	39	22	61	61	
Infection of pulp					
(a) Uncomplicated	27	33	37	60	4 not known (ceased attendance) 48 for 2 to 3 weeks 8 for 4 to 8 weeks
(b) With necrosis of terminal phalanx	5	7	9	12	2 not known (ceased attendance) 2 for 6 weeks 2 for 8 weeks 6 for 12 weeks
Total infection of pulp	32	40	46	72	
Paronychia					
(a) Uncomplicated; acute	32	52	42	84	6 not known (ceased attendance) 4 for 1 week 62 for 2 to 3 weeks 12 for 4 to 6 weeks
(b) With infection of pulp	2	6	6	8	5 for 3 to 5 weeks 3 for longer than 5 weeks
(c) Chronic and recurrent	2	7	1	9	From 5 weeks to 6 months
(d) Pus under distal part of nail	4	9	8	13	12 for 1 to 3 weeks 1 for 5 weeks
Total paronychia	40	74	57	114	
Subcutaneous abscess and cellulitis of fingers	54	35	58	89	3 not known (ceased attendance) 4 for 1 week 55 for 2 to 3 weeks 27 for longer than 3 weeks
Carbuncle of fingers or hand	6	0	1	6	1 for 2 weeks 5 for 3 to 4 weeks
Palmar and web abscesses	13	7	12	20	3 for 1 to 2 weeks 12 for 3 to 4 weeks 2 for 6 weeks 1 for 8 weeks 2 for 11 weeks
Infection of the flexor tendon sheaths	4	4	8	8	1 not known (ceased attendance) 1 for 2 weeks 6 for 8 weeks and longer
Suppurative arthritis	6	3	9	9	1 not known (ceased attendance) 1 for 2 weeks 6 for 8 weeks and longer
Miscellaneous	1	6	1	7	
Total cases	195	193	253	388	

As may be seen in table 4, necrosis of the terminal phalanx complicating infection of the pulp more than doubles the period of disablement and often leaves the patient with some permanent defect; the sensitive pulp of the finger is usually destroyed. In such cases there was always either a long interval between the onset of pain and the

patient's attendance at the hospital (from nine days to four weeks), or there was a history of two or more operations, which suggested that the first operation either was mistimed or was inadequate. One patient had his finger incised three times by his physician and twice at the hospital before the remnants of the phalanx were amputated.

Of the cases of infection of the flexor tendon sheaths, the diagnosis in 1 was doubtful. The patient was treated with rest and hot fomentations, and the condition, which was perhaps cellulitis, subsided without an operation. Of the 6 cases in which operation was performed, the injury was a cut in 3 instances and a penetrating wound in the others. The periods elapsing between the injury and the patient's admission to the hospital were eleven, fourteen, unrecorded, three, five and fourteen days, respectively. In 3 cases the infection was probably primarily in the tendon sheath; in the others infection in the tendon sheath complicated cellulitis of the finger in 2 and an infection of the pulp in the third. In all 6 the diagnosis was confirmed at operation, and in all these the tendon sloughed. In 2 the finger was eventually amputated, and in all 6 there was severe permanent damage to the hand. The periods of disablement in the cases in which the affected finger was amputated were five and one-half and four months. In 3 other cases, eight, ten and twelve weeks elapsed before the wounds were healed. One patient ceased attendance at the end of eight weeks, with an unhealed wound.

In the cases of suppurative arthritis the joints affected were: the interphalangeal joint of the thumb in 2, the distal interphalangeal joint of the finger in 1, the proximal interphalangeal joint of the finger in 5 and the metacarpophalangeal joint of the finger in 1. Table 3 shows that the thumb and the index and the middle finger were the digits affected. There was a history of injury in all, and the arthritis complicated an infection of the pulp in the first 3 mentioned and cellulitis of the finger in the others. In all there was roentgenologic evidence of osteomyelitis of one or both bones forming the joint. In 1 case the finger was amputated, and the period of disablement was three months. Two patients ceased attendance when they still had sequestrums and discharging sinuses. Two patients had periods of disablement of six weeks, but 1 of these, although he was back at work, had a stiff, painful thumb. Two women had periods of disablement of ten weeks. In both the pulp of the finger had been infected, and in both hyperesthesia of the scar appeared, persisting in 1 case for one year and in the other for eight months. In the remaining 2 cases the periods of disablement were eleven and fifteen weeks, and although there was considerable limitation of movement of the affected joints, the function of the hand was good. With the exception of these 2, all the patients were left with some permanent damage to the hand.

TABLE 5.—*Cases in Which the Usual Period of Disablement Was Exceeded*

Cases	Period of Disablement	Cause or Supposed Cause of Prolongation
Injury by crushing		
Usual period of disablement 1 to 4 weeks		
1 to 3	6 to 7 weeks	Infection of wound
4	10 weeks	Infection of wound complicated by suppurative arthritis of terminal interphalangeal joint
5	13 weeks	Infection of initially unrecognized compound fracture of terminal phalanx, leading to necrosis of phalanx and sequestration
6	2½ years +	Slight initial infection of wound followed by causalgia
Other injury		
Usual period of disablement 1 to 4 weeks		
1	5 weeks	Subcutaneous abscess of palm from which a needle was removed; injury was a lacerated finger, healed in 3 weeks
2	7 weeks	Stiff fingers
3	10 weeks	Infection of wound and necrosis of terminal phalanx
4	10 weeks	Hyperesthesia of scar
5	6 months	Partial dry gangrene developed during treatment for compound fracture of phalanx; refused amputation
Uncomplicated infection of pulp		
Usual period of disablement, 2 to 3 weeks		
1 and 2	4 to 5 weeks	None found
3	5 weeks	Previous infection of pulp in same finger 8 years before; bone in old scar
4 to 6	6 to 7 weeks	Delay in starting treatment; interval of 10 to 18 days between onset of pain and hospital attendance
7	7 weeks	Inadequate or mistimed operation; two operations
8	8 weeks	Inadequate or mistimed operation; three operations; hyperesthesia of scar
Infection of pulp with necrosis of terminal phalanx		
Shortest period of disablement, 6 weeks		
1 to 2	12 weeks	Hyperesthesia of scar
Paronychia, uncomplicated, acute		
Usual period of disablement, 2 to 3 weeks		
1 to 5	4 to 5 weeks	None found
6 and 7	5 and 6 weeks	Delay in starting treatment; interval of 7 and 14 days between onset of pain and hospital attendance
8 to 11	5 to 6 weeks	Inadequate primary operation for removal of nail; second operation
12	6 weeks	Raynaud's disease
Paronychia, complicated by infection of pulp		
Usual period of disablement, 3 to 5 weeks		
1	6 weeks	Delay in starting treatment; interval of 7 days between onset of pain and hospital attendance
2	10 weeks	Inadequate or mistimed operation; four operations
3	11 weeks	Patient stopped attendance for 4 weeks and on return had necrosis of terminal phalanx
Pus under distal part of nail		
Usual period of disablement, 1 to 3 weeks		
1	5 weeks	Splinter buried in nail bed, overlooked at first operation
Cellulitis and subcutaneous abscess of fingers		
Usual period of disablement, 2 to 3 weeks		
1 to 13	4 to 6 weeks	None found
14 to 20	4 to 6 weeks	Inadequate or mistimed operation; two or more operations
21 to 23	4 to 6 weeks	Delay in starting treatment; interval of 7 to 10 days between onset of pain and hospital attendance
24	3 months	Inadequate or mistimed operation; two operations
25	3 months	Stiff finger
26	3 months	Initial lymphangitis; appearance of residual brachial abscess 2 weeks after cellulitis of finger had subsided
27	4½ months	Gangrene of finger with severe infection of hand; cause unknown
Palmar and web abscess		
Usual period of disablement, 3 to 4 weeks		
1 and 2	6 weeks	Both deep abscess of palm; for 1, two operations
3	8 weeks	Deep abscess of palm; initial incision wrongly made on dorsum
4	11 weeks	Web abscess with splinter in hand, stated to have been removed, but finally discharged spontaneously
5	11 weeks	Hyperesthesia of scar
Suppurative arthritis		
Shortest period of disablement, 6 weeks		
1	8 months	Apparently permanent hyperesthesia of the scar in both cases
2	1 year	

Of the patients with miscellaneous lesions 1 was a woman aged 20 who had had a chronic ulcer on the dorsum of the ring finger for four weeks when she was first seen. She was treated for another four weeks without improvement, after which, on curettage, a splinter was found, and two weeks later the ulcer had healed.

Table 5 shows the cases in which the usual period of disablement was exceeded; the cause, or supposed cause, of this is indicated. In cases of injury, infection of the wound, and in cases of whitlow, delay in starting treatment, mistimed or inadequate operation and hyperesthesia of the scar were most commonly responsible for this prolongation.

COMMENT

The well known association of trivial injury with infection of the hand is illustrated by the figures given in an early part of this paper. It is likely that if such injury were to receive prompt treatment the incidence of whitlow would be much reduced. This supposition has been confirmed within my own knowledge by the experience of a large engineering firm, which found that the strict application of prophylactic measures to trivial cuts and scratches was followed by a material reduction in the incidence of infection. Such measures are immediate cleansing of the wound, its protection against contamination and a warning to the patient to report immediately if the lesion becomes painful.

With regard to acute infection, certain tendencies in treatment seem to be emerging from physicians' experience, though they cannot yet be looked on as established. They may be stated thus:

1. Operative treatment, short of total extirpation of the affected area, cannot benefit a patient with an acute infection during the period of spread. There is no clear evidence that the supposed "relief of tension" effected by a premature incision ever checks the progress of an infection, whereas such incision almost always preciptates sloughing and actually increases the amount of damage.

2. The function of operation is the evacuation of pus, and it is as important to avoid undue haste in operating as to avoid undue delay.

3. In the early stages treatment must be directed to helping the tissues in their struggle with the infection. The most important elements in this are elevation and absolute immobilization of the limb.

4. While rest is of the greatest value during the stage of acute invasion, it must be discontinued as soon as healing has begun. Disuse of a finger itself may produce serious disablement.

At present too much stress is perhaps laid on the anatomic basis of the treatment of these conditions. Attention is so much focused on the site of the incision and the necessity for early operation "to relieve

tension" that unnecessary operations are apt to be encouraged. It is necessary to state emphatically that premature incision for spreading cellulitis is by no means a harmless blunder; it may determine the onset of sloughing. The plea for early incision is usually stressed in cases of infection of the digital pulp, and it is stated that unless tension is relieved dire results follow. It is certainly more difficult to abort an infection of the pulp than to arrest cellulitis elsewhere in the hand, but this is probably due to the situation of the pulp at the end of the arterial tree of the upper limb. Premature incision for cellulitis of the pulp is thus more likely to result in extensive sloughing and may possibly cause necrosis of the terminal phalanx. It is only recently that strict immobilization of the affected hand has been insisted on, yet during this time, in several cases established infection of the pulp has subsided without operation. In others the infection has progressed to abscess formation and has yielded to simple incision, and in none has any serious complication developed.

Immobilization is secured by means of light metal or plaster splints, and swelling and congestion of the inflamed area are reduced to a minimum by elevation of the limb. This is best done with the patient in bed, but when this is impracticable the next best thing is to keep the hand near the opposite shoulder by means of a sling. The method of splinting or elevation must not interfere with the circulation, and care always should be taken that there is no possibility of this. Should operation be necessary, after-treatment should consist of the twice daily application of hot fomentations to prevent the incision from crusting over and care that the patient carries out active movements of the unaffected fingers.

There is one important point which remains, that is, the relation of disuse to the function of the hand. The hand seems to be dependent for efficiency on constant use. Complete disuse, whether produced by therapeutic immobilization or by a tender scar, is followed by atrophic changes in the fingers, which result in their disablement. This may be prevented in the former instance by discontinuing immobilization and by starting active movements as soon as healing is established. In the latter, in which the condition is more difficult to deal with, the tender area must be protected by some form of shield and the patient made to use the finger. It is important that this should be done as soon as possible; therefore, after the wound has healed, every patient is examined to determine the mobility of the fingers before he is finally discharged.

TREATMENT OF INTESTINAL OBSTRUCTION

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Recently Aird, of Edinburgh, stated that since the beginning of the century the mortality from intestinal obstruction has remained about 40 per cent. He added that despite animal experimentation, the knowledge acquired in this field has not been sufficiently applied to therapy. When one considers that intestinal obstruction is one of the most common occurrences, if not the most common, at least in the surgical clinic of Professor Delrez, and when one reflects on the high mortality reported by Aird, one is not surprised at the efforts of clinicians to improve the treatment for this grave condition.

I wish particularly to emphasize that obstruction is rarely a disease per se. It is as a rule the consequence of a preexisting condition or of a malformation, or the cause may remain obscure. But in all instances the obstruction aggravates further the original condition. One should, however, in the presence of obstruction, forget the immediate or the remote cause and employ all one's efforts to relieve the obstruction. I shall attempt to relate my conception of the treatment of intestinal obstruction and to base it, so far as possible, on physiopathologic considerations as gained from experience.

The influence of the French and the German contributions resulted in the concept that intestinal obstruction produces intoxications of various kinds. Since 1912, the American school, represented by Hartwell and Hoguet and later by Haden and Orr, whose precursors in France included such men as E. Vidal and Delore, has changed this point of view, for these men regarded death following intestinal obstruction as due primarily to anhydremia and hypochloremia. A tendency developed to ignore the toxic aspect of the problem and to consider anhydremia and hypochloremia as the only factors causing death from intestinal obstruction, at least from high intestinal obstruction. I feel that if one wishes to study all the aspects of the problem it is necessary to modify this method of interpreting the phenomena. It is much more likely that intestinal obstruction produces an intoxication first of the blood and then of the tissues. This intoxication may have several places of origin, such as the obstructed intestine or the pancreatic gland, as demonstrated by the favorable results obtained in animals when the pancreas is short-circuited, even though one cannot explain the manner in which this

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occurs. The liver likewise may have something to do with the toxic phenomena. Besides this toxemia, there develop factors of great importance, factors to which I have given the names of dehydration and demineralization of the blood and tissues. These factors alone may account partly for a particular toxemia, to the exclusion of the obstructed intestine. As a matter of fact, dehydration and demineralization result in a reduction of the volume of the blood and the arterial pressure, in consequence of which there is an alteration in the tissue circulation of the type which permits the cellular metabolites, some of which are highly toxic, to be only imperfectly removed by the blood. The result is tissue intoxication. On the other hand, the metabolites taken up by the blood are only imperfectly eliminated owing to a diminished excretion of urine, which in itself is the result of dehydration and demineralization. The result is a toxemia dependent solely on dehydration and demineralization. However, these two factors are not the only ones involved in intestinal obstruction, for if one supplies only the elements lost by dehydration and demineralization one obtains only incomplete benefit from the therapy. In order for this form of therapy to be of value, one ought to give the patient a quantity of water and of mineral elements much greater than would be necessary to make up for the losses caused by vomiting, diuresis, sweating and respiration. To recapitulate briefly, intestinal obstruction results in a toxemia, all the effects of which are made possible by dehydration and demineralization, the latter being capable in themselves of producing a part of the intoxication. I do not ignore the importance of the level of the obstruction, for I realize that the gravity of symptoms depends on its height. The intoxication, however, though obscured by the symptoms of dehydration and demineralization and not recognizable on superficial examination, remains the primary cause of the severe manifestations accompanying intestinal obstruction. The foregoing facts should serve as a guide to the choice of efficient therapy, which I shall now discuss.

TREATMENT

Certain principles in the treatment of intestinal obstruction may be considered as fundamental. If the patient's condition is not too grave and operation may be postponed for several hours, it is advisable to restore the water and minerals that have been lost. This treatment consists in furnishing the body with water in large quantities and with simple ions, particularly chlorine, sodium, potassium and calcium, in an isotonic or mildly hypertonic solution. The fluids may be administered subcutaneously or intravenously. If the condition of the patient is grave and immediate operation is indicated, this form of therapy is impossible.

Anesthesia.—The choice of anesthesia is one of the most important problems in the treatment of intestinal obstruction. One should not lose sight of the fact that the obstruction causes a toxemia, and that one should not introduce a new toxic substance into the blood stream. Local, or regional, anesthesia is the best, and it has been used in the majority of cases which I have observed at the clinic. It goes without saying that this type of anesthesia is not applicable in every case. Under certain conditions I have used spinal anesthesia, generally induced with procaine hydrochloride, with satisfactory results. I feel, however, that spinal anesthesia should not be used for the toxic patient whose arterial pressure is already very low. I shall discuss spinal anesthesia later. If local anesthesia is not sufficient, it may be supplemented with ether during the painful steps of the operation. Certain anesthetics must be used with caution. This applies particularly to anesthetics introduced intravenously or by rectum. These anesthetics when introduced into the circulation may not be well tolerated, because of hepatic changes and consequent reduction in the antitoxic function of the liver and because of diminished excretory function of the kidney. To sum up, I advise the choice of the most innocuous anesthetic, and I cannot sufficiently emphasize the advisability of local or regional anesthesia whenever possible.

Operation.—The essential principle in the treatment of intestinal obstruction is always to practice the simplest kind of operation. I have already stated that intestinal obstruction cannot be called a malady per se but is the consequence of some other preexisting lesion. It is the obstruction, however, that should always be treated. It alone constitutes an emergency. The aim of the treatment is to remove the obstruction by the simplest means. If the patient's general state permits, I treat both the obstruction and the primary cause by instituting a complete operation. Experience, however, teaches that frequently a simple operation will save a life and will permit later treatment of the causative lesion under much better conditions, while a complicated operation which relieves the obstruction and the cause results in a large number of fatalities from various complications developing a few days after the intervention. I shall refer again to the fact that the simplest operation will relieve the obstruction and that few of the patients operated on die of the effects of obstruction. However, when one practices resection and suturing of the obstructed bowel, one may expect some disagreeable complications, despite the fact that the obstruction is relieved. No tissue is less suitable for suturing than an intestine which is the seat of an obstruction. Therefore, the important principle to be applied as far as possible is to relieve the obstructon by the simplest operative technic.

Postoperative Treatment.—Frequently the most important part of the operation is the after-treatment, concerning which the following sug-

gestions are made. Rehydration and remineralization should be accomplished through injections of large amounts of isotonic or mildly hypertonic solutions of chlorine, sodium, potassium and calcium by the subcutaneous, intravenous, rectal and, if possible, oral route. This treatment has two aims, namely, to remove rapidly the toxins which tend to overwhelm the organism by instituting a satisfactory diuresis and to improve the function of the skin; in addition, the bowel functions much better when the water supply and minerals have been restored. In order for this treatment to be effective, however, one should introduce large amounts to replace the fluids lost. I have found it advantageous in some cases to wash out the stomach several hours after the operation. A certain amount of toxic material is thus removed from the gastrointestinal tract. The lavage has to be repeated only exceptionally. Symmonds advised encouraging vomiting after the operation. I prefer lavage. Some clinicians advise duodenal suction. This is an ancient method which was practiced on animals in 1767 by Monro, an English veterinarian. It was used in man by Kussmaul in 1867, with varying results. It was reintroduced by Wangensteen and Paine in 1933, and recently Paine has perfected the apparatus for aspiration. I have had no experience with this method and have not resorted to it in a single case.

I have summed up rapidly the principles which should be followed in the treatment of intestinal obstruction. I shall now describe with some detail the various forms of obstruction treated for the past six years in the surgical clinic of Professor Delrez. This experience includes 334 cases of obstruction.

MECHANICAL OBSTRUCTIONS

Congenital Stenosis and Atresia; Imperforate Anus.—A 4 day old infant with congenital atresia of the large intestine was treated by creating a fistula in the small intestine, but the child died. An infant 4 months old had imperforate anus combined with a perineal fistula, and 2 infants, each 1 year of age, had imperforate anus with a rectovaginal fistula. The treatment consisted of dilation of the anus and reduction of the rectal ampulla. The 3 infants survived, although a small rectovaginal fistula persisted in 1.

Obstruction by Foreign Bodies.—One patient had an obstruction at the level of the ileocecal valve due to undigested food. Enterostomy was performed, the intestine was emptied of its contents and the opening was closed; the patient recovered. In 1 patient the obstruction was due to ascarides. At laparotomy pressure was exerted on the bowel so that the ascarides passed on toward the cecum; the patient recovered. A sponge left in the abdomen at laparotomy was the cause of intestinal

obstruction in another patient; removal of the sponge brought about relief.

Inflammatory Tumors.—One patient with an inflammatory tumor of the cecum recovered after drainage. Another patient had stenosis due to a bacillary infection of the middle portion of the small intestine; perforation occurred, and resection with end to end anastomosis was performed. The patient died three weeks later from a pulmonary abscess. One patient with stenosis of the small intestine, caused by tuberculous infiltration of the intestinal wall, was subjected to resection and end to end anastomosis, with recovery. Another with a tuberculous cecum and complete obstruction was subjected to hemicolectomy on the right side followed by ileocolostomy and died three weeks later as a result of a pulmonary abscess. A patient with tuberculosis of the splenic flexure died twenty-four hours after simple exploratory laparotomy. Finally, a patient with obstruction of the small intestine due to a caseating mesenteric gland, 30 cm. above the cecum, was subjected to partial excision of the node; he survived the drainage but died later.

Neoplasms.—There were 2 patients with obstruction of the small intestine due to carcinomas. Resection of the tumor followed by end to end anastomosis was performed on the first patient under spinal anesthesia; death was due to peritonitis. Nothing more than an exploratory laparotomy could be performed on the second patient because of the dissemination of the cancer. Of 5 patients with tumors of the cecum, 4 were subjected to resection of the tumor followed by ileocolostomy under ether anesthesia. One of these 4 patients died of peritonitis, 1 died of pneumonia and the other 2 survived. The fifth patient survived after the creation of a fistula of the small intestine. Two patients with tumor of the ascending colon were subjected to hemicolectomy on the right side followed by ileocolostomy with recovery, though a fecal fistula persisted in 1. A third patient was treated by exteriorization of the tumor and resection. The medially placed anus was closed at a second operation, but a small fistula persisted. The three operations were performed with the patients under ether anesthesia. Six patients with carcinoma of the transverse colon were treated in the following manner: Four underwent cecostomy, 2 under local anesthesia and 2 under ether anesthesia. All 4 recovered. Two underwent resection with end to end anastomosis of the transverse colon, 1 under local anesthesia and the other under ether; 1 died of peritonitis. There were 6 patients with carcinoma of the splenic flexure. Three underwent cecostomy, 2 under local anesthesia; 2 of the 3 died later, 1 of multiple abscesses which developed in the tumor. An artificial anus was made in the transverse colon of 1 patient under local anesthesia;

death resulted from peritonitis. The 2 remaining patients were treated by exteriorization followed by extraperitoneal removal of the tumor and closure of the artificial anus. Ether anesthesia was used in 1 and procaine hydrochloride administered spinally in the other. Both recovered.

There were 20 patients with carcinoma of the sigmoid flexure. Nine were operated on under local anesthesia, 5 under spinal anesthesia with procaine hydrochloride and 1 under spinal anesthesia after the method of Jones. For 1 Schleich's anesthetic mixture was used, for 1 Schleich's mixture plus oil of cajeput, for 1 ether and for 1 chloroform.

The following types of operations were performed: creation of an iliac anus, 10 cases; exteriorization and removal of the tumor, 4 cases; exteriorization and extraperitoneal removal of the tumor with closure, 3 cases; exteriorization and intraperitoneal removal of the tumor with closure, 2 cases, and creation of a fistula in the terminal portion of the ileum, 1 case.

Seven of the patients in whom an iliac anus was made died between the eighth day and the third month after the operation; 2 of those on whom exteriorization was performed died between the fourth and the fifteenth day.

There were 49 patients with cancer of the rectum. Thirty-six were operated on under local anesthesia and 1 under spinal anesthesia with procaine hydrochloride. For 10 ether was used, for 1 Schleich's mixture plus oil of cajeput and for 1 a preparation of ethyl chloride locally.

A simple iliac anus was created in 29 cases; an iliac anus was created followed by sacroperineal resection in 15 cases, and abdominal perineal resection was done in one stage in 5 cases.

Six of the patients in whom an iliac anus was made died between the third day and the third month after the operation, from various causes. Four of those subjected to abdominal perineal resection died from one to ten days after intervention.

Membranous Enterocolitis.—Of 2 patients with membranous enterocolitis, 1 recovered on medical treatment and the other died of peritonitis five days after cecostomy.

Duodenal Obstruction.—In 1 patient who had undergone gastroenterostomy for a gastric ulcer obstruction caused by the trunk of the mesenteric artery developed at the junction of the superior two thirds and the inferior third of the duodenum. Duodenojejunostomy was performed with the patient under ether anesthesia, and death occurred on the fifteenth day.

Obstruction Due to Adhesions.—There were 4 patients who had adhesions of congenital origin. In 1 compression of the intestine was

caused by a branch of the mesenteric artery, which produced anemia of the intestinal loop and a consequent obstruction. There was 1 patient with obstruction due to Meckel's diverticulum and 13 with obstruction due to postoperative adhesions (following appendectomy, operation for perforated ulcer, hysterectomy and operation for strangulated hernia). Twelve of the patients were treated by division of the adhesions, 1 by division of the adhesions and drainage, 3 by enterostomy and 1 by side to side anastomosis. One patient was kept on a milk and ice cream diet.

Two of the patients died after division of the adhesions, 1 after division of the adhesions and drainage and 1 after side to side anastomosis.

The most favorable operation, without doubt, is that of a simple division of the adhesions. However, it is not always sufficient and must be supplemented by anastomosis or resection followed by anastomosis, which makes the prognosis more grave. In certain cases the adhesions cannot be divided and one has to be satisfied with enterostomy either on the loop just above the obstruction or more frequently on the first presenting loop. This operation may be radical. After the release of the intestine and relief of the obstruction, detoxification of the patient is instituted and the fistula closes spontaneously or is closed by the surgeon. More frequently the obstruction persists. On rehydration of the patient, the fistula may close spontaneously. More frequently the obstruction may be removed by operation when the patient's state has improved. If the obstruction persists, a second enterostomy is performed in order to improve the general state of the patient, and the obstruction is later treated operatively. In any event, an enterostomy is not the most satisfactory procedure, but it enables one sometimes to save the life of a patient who could not withstand a severe operation.

I shall add to this group of cases those of intestinal obstruction due to bacillary peritonitis, of which there were several. Nine patients with fibrous adhesive peritonitis were treated in the following manner: 1 by ultraviolet irradiation, 4 by simple laparotomy, with 2 deaths; 1 by laparotomy, drainage and roentgen irradiation, with the development of a stercoraceous fistula and death after two and one half months; 1 by laparotomy, drainage and ultraviolet rays; 2 by laparotomy and freeing of the adhesions and 1 by laparotomy, freeing of the adhesions and ultraviolet irradiation.

Nine patients with peritonitis of the ascitic type were treated in the following manner: 1 by simple heliotherapy; 4 by laparotomy and exposure to air, with 1 death; 1 by laparotomy, exposure to air and peritoneal lavage with oil of cajeput; 2 by laparotomy, drainage,

exposure to air and postoperative treatment with ultraviolet irradiation and 1 by laparotomy, exposure to ultraviolet rays during the operation and postoperative treatment with ultraviolet rays.

Obstruction Due to Compression of the Intestine.—There was 1 patient with obstruction of the splenic flexure caused by hypertrophy and ptosis of the spleen. The obstruction was removed by splenectomy. Two patients with obstruction in the course of pregnancy were subjected to exploratory laparotomy, after which the obstructive phenomena disappeared.

Strangulated Hernias.—There were 141 patients with strangulated hernia, including those of the inguinal, femoral, umbilical, epigastric and ventral types. One hundred and twenty-five of these were adults between 16 and 87 years of age, and 16 were infants from 5 months to 5 years of age. The duration of the strangulation varied from four and one-half hours to seven days. Taxis was practiced on 10 adults and 1 infant. One death occurred on the sixth day, from cerebral hemorrhage with uremia. The results in another case were very instructive. After an unsuccessful attempt was made for about twelve minutes to reduce the hernia by taxis, an operation was decided on, and spinal anesthesia was induced with procaine hydrochloride. Before the operation the hand was placed over the hernia, and mild compression of the hernial contents resulted in their reduction. The patient no longer experienced any pain. It was decided not to operate. On the following day pains returned. Laparotomy revealed a properly reduced hernia with one intestinal loop badly injured and perforated. The patient died. This accident emphasizes that one should be very cautious in the practice of taxis. I did not consider the efforts employed sufficiently rough to cause perforation of the intestine. On the other hand, the strangulation did not last more than three hours and I had every reason to believe that the vitality of the intestine was not compromised. There was no reaction of any kind in the vicinity of the strangulation. It is probable that the spinal anesthesia caused relaxation of the abdominal wall and permitted the reposition of the intestine, which perforated later. Leriche stated that although intestinal obstruction may be relieved by spinal anesthesia, such relief is not to be relied on. I shall speak of this later. Another disadvantage of the method of taxis consists in the possibility of reducing the hernia en masse. It permits of the continuation of obstruction and only delays the operation. To sum up, one should be extremely careful in performing taxis.

One hundred and thirty patients with strangulated hernia were subjected to operative intervention. Thirteen infants were operated on under ether anesthesia and 2 under chloroform. Nine adults were

operated on under ether anesthesia, 2 with chloroform, 1 under Schleich's anesthesia and 1 with Schleich's mixture plus oil of cajeput. The remaining 106 patients were operated on under local anesthesia induced with 1 or 0.5 per cent procaine hydrochloride in amounts of from 30 to 50 cc.

I have employed, as a rule, a very simple technic, the Bassini or the Forgue method for inguinal hernia, Ruggi's method for femoral hernia and a simple reenforcement of the abdominal wall for umbilical or epigastric hernias or eventrations. The intestine, even though considerably altered, assumes a rosy coloration and manifests a few contractions after the application of warm physiologic solution of sodium chloride and is then returned to the abdomen. Of 28 patients operated on for this condition, 5, all adults of advanced age, died. One had a strangulated femoral hernia of five days' standing with a beginning gangrene of the bowel and intestinal paralysis; another had a femoral hernia of twenty-four hours' duration and died ten days later from pulmonary abscess; another patient died as the result of acute pulmonary edema; the fourth died of peritonitis despite the fact that the bowel did not appear much altered at the time of operation, and, finally, the fifth died from an unknown cause. In 10 cases a complicated procedure was carried out: In 2 instances the perforated herniated intestinal loop was sutured and the patients recovered. In 1 case the loop was sutured and attached to the neck of the sac. In 1 case the intestinal loop was exteriorized and resected; the two lumens were sutured to the skin, end to end fashion; death took place after twelve days. In 4 instances enterostomy was performed on an exteriorized bowel; 3 patients died, and 1 recovered with a fistula, which was later closed. Twice resection of the loop and intestinal anastomosis was practiced; in both instances the patient died.

It is evident that the simple operations offer a greater chance of saving the life of the patient with a strangulated hernia than the complicated operations, which are followed by a considerable mortality. Finally, I wish to mention 1 case of strangulated hernia in which phenomena of obstruction developed one month later as a result of a plastic peritonitis and which necessitated intestinal resection. The patient recovered.

Volvulus.—There were 4 patients with volvulus. One, a 4 day old infant with volvulus of the small intestine, resulting in necrosis of the loop, underwent resection with an end to side anastomosis which proved fatal. Two patients with volvulus of the cecum, of the ascending colon and of the sigmoid flexure in whom untwisting was performed recovered. Finally, the last patient was admitted to the clinic in a moribund condition as a result of volvulus of the ascending colon. No treatment was attempted.

Intussusception.—There were 10 patients with intussusception. In 2 the small intestine was involved; in 1 resection followed by an end to end anastomosis was successfully practiced. The other patient died. Autopsy revealed a reduced intussusception followed by fixation of the loop to the parietes. Seven patients with ileocolic intussusceptions were operated on. For 5 ether anesthesia was used, for 1 chloroform and for 1 Schleich's mixture plus oil of cajeput. Reduction of the intussusception followed by ileocolopexy was practiced. In 1 case a simple reduction was done. One death resulted from hyperthermia. One patient survived after the reduction of a colocolonic invagination. In 1 case of ileocolic invagination an attempt at reduction was made by means of an enema of barium sulfate. The invagination was successfully reduced, but it recurred two days later and operation was necessary. The principle of this method is old. It originated, as a matter of fact, with Hippocrates, who practiced it in the treatment of intussusception and particularly of certain forms of intestinal obstruction. He recommended introduction into the anus of large quantities of air by means of a sound or a tube, and when the abdomen became sufficiently distended the tube was removed and water was introduced immediately after. Hippocrates claimed to have brought about a cure in that fashion in many cases of invagination.

I have recorded 55 fatalities among 302 patients with mechanical obstruction, a percentage of 18.25, which is a relatively small mortality. I particularly emphasize the fact that the cause of death in the majority of instances was not the obstruction. All patients operated on, with the exception of 4 or 5, were relieved of the obstruction in the course of the operation, with reestablishment of the fecal current, death supervening as a result of various conditions, some of which were undoubtedly favored by the obstruction. On the other hand, a study of the postoperative deaths in the cases of carcinoma of the sigmoid flexure and of the rectum and above all in the cases of strangulated hernia, reveals that the safety of the patient lies in the less complicated operations. Therefore, in the presence of a mechanical obstruction of the intestine the first concern should be that of saving the life of the patient. One should not resort to complicated operative procedures but should postpone the removal of the cause of the obstruction to the time when the patient has been relieved of his toxemia, anhydremia and loss of minerals.

FUNCTIONAL OBSTRUCTIONS

Functional obstructions present an entirely different story. First, the etiologic factors are unknown in most of the cases, and even if under certain conditions the primary cause of ileus is found, it is impossible to establish the relation of cause and effect. This lack of knowledge is due to ignorance concerning the role of the innervation of the

intestine in man. Neither the physiologists nor the clinicians possess an accurate idea of the physiology of intestinal innervation. The methods of study have not been effective. By one of the methods a small portion of the intestine is removed from an animal or from a human being and placed in a nutritive solution or is nourished by defibrinated blood with the addition of different chemical substances. Such a method cannot possibly give one any idea of the conditions in vivo or in situ, either in the normal state or under pathologic conditions, and cannot be used to elucidate the physiology of intestinal innervation. The only permissible method is to study the bowel in situ or in a living animal, and here one immediately runs into insurmountable difficulties. If one wishes to investigate the role of innervation of the intestine one should theoretically be able to deprive this viscus of its nerve supply. It can readily be seen that this cannot be accomplished, because it implies the removal not only of the sympathetic trunks and the pneumogastric and the intermediary ganglionic plexuses but of the intramural plexuses of Auerbach and Meissner. It can readily be understood that such a performance is impossible and that because of the autonomic character of the bowel complete denervation cannot be obtained. Lack of knowledge relative to the role of innervation of the intestine in the normal or pathologic state is responsible for the uncertainty in which one finds oneself when considering the field of paralytic ileus from a pathologic standpoint. Moreover, mechanical obstructions may be complicated by functional phenomena. Occasionally in strangulated hernias an entire loop of intestine is not found in the hernial sac, but only a piece of compressed omentum or a small pinched-off portion of the lateral antimesenteric border of the intestine. I have seen 2 cases in which the lumen of the entire intestine was patent and in spite of it there existed an obstruction which disappeared when the omentum was released or when the lateral pinching was removed. The remarkable thing in such cases is the total obstruction such as follows strangulation of the entire loop. This observation makes it probable that there exist centripetal influences concerning the intestinal innervation, in spite of the fact that this is contradicted by certain physiologists.

I shall consider briefly a few examples of functional ileus that I have observed. I have stated that mechanical obstruction is, as a rule, secondary to some preexisting condition. Only when an obstruction is produced is one compelled to turn one's attention to the original cause, and one should attempt to remove the obstruction before anything else. Functional ileus may likewise be secondary to an original condition, but in a great number of cases it is the latter which presents all the signs and the treatment of which results in the amelioration or cure of the condition. Such is the case with obstructive phenomena

which accompany inflammatory processes of the abdominal viscera (appendicitis, cholecystitis, salpingitis, pancreatitis, perforation of an ulcer, renal diseases).

I shall not discuss these forms of obstruction here. With these conditions, therapy is directed to the cause.

Inflammatory Obstructions.—Obstructions of this type are secondary to peritonitis and develop some time after an abdominal condition. I have observed 2 cases of peritonitis secondary to perforation of an ulcer. Drainage was established in 1 case, and the patient died six days later; in the other case the patient received symptomatic treatment only and died at the end of twenty-four hours. In 3 cases peritonitis followed appendicitis of several days' standing for which operation had not been performed. The treatment consisted of appendectomy and drainage. The patients recovered. I have had 7 patients between the ages of 57 and 85 who presented blood urea concentration of from 1 to 6 Gm. per hundred cubic centimeters. Only 1 patient survived and for this one the treatment consisted of restoration of the fluids and minerals on a massive scale. The other 6 patients were treated as follows: Three were subjected to an exploratory laparotomy, 1 to the establishment of an iliac anus and 2 to lavage combined with extensive bleeding. All died between forty-eight hours and twenty-eight days after the institution of treatment. The exploratory laparotomies revealed general dilatation of the entire intestine without any obstruction to the fecal current. I believe that the patients died not from the obstruction but from uremia, since in the majority of the patients treated the fecal current was reestablished. I feel that the best treatment for this obstruction is copious rehydration and remineralization.

Lead Poisoning.—Two patients suffering from saturnism presented functional spastic obstruction. They recovered with treatment of the saturnism by removal of the lead and administration of a milk diet and potassium iodide.

Coronary Thrombosis.—A patient suffering from coronary thrombosis of the anginal type presented genuine complete paralytic obstruction. The obstruction was relieved by enemas and hot applications. Four days later the patient suffered another attack of angina and died. Postmortem examination revealed an infarct of the myocardium.

Intestinal Worms.—One patient presented a functional intestinal obstruction of the spastic type, which was found to be due to intestinal parasites. The obstructive crises disappeared in the course of treatment. Perhaps this obstruction was of the type described by Rost and attributed to substances secreted by the genital and digestive organs of the parasites and producing a condition of the bowel. The treatment directed toward the removal of the parasites was followed by the disappearance of

obstructive crises, but nothing justifies my saying that the relation exists between the worms and the obstruction.

Acute Alcoholism.—A patient presented characteristic symptoms of intestinal obstruction following a drunken orgy. The use of enemas and a diet gave relief.

Tabes.—A patient suffering from tabes and subject to obstructive phenomena of paralytic nature was subjected to an exploratory laparotomy, which failed to reveal the existence of any lesion. The crises disappeared after antisyphilitic treatment.

Hysteria.—Two hysterical patients presented symptoms of paralytic obstruction. Treatment of their nervous manifestations was effective in curing the obstruction.

Functional Ileus of Unknown Cause.—In 12 patients I observed intestinal obstruction of spastic or of paralytic nature; at times the spastic and the paralytic phenomena alternated. I have searched in vain for the cause of this type of obstruction. One patient had a thrombosis of the left external iliac vein. The rest of the patients presented nothing abnormal but the obstruction. Seven patients were treated medically by enemas and laxatives, with recovery. Five were subjected to operation. The 3 who underwent exploratory laparotomy died in from twenty-four hours to seventeen days after the operation. One patient on whom cecostomy was performed, and another on whom enterostomy of the small intestine was done died twelve and fifteen days later, respectively, in spite of the fact that the obstruction was relieved. To sum up, there were 9 deaths in 32 cases of functional obstruction, or 28 per cent. It appears that one should be careful about operating in cases of obstruction which is the result of peritonitis. Operative intervention on uremic patients with obstruction or on patients with functional obstruction of unknown cause gave bad results, despite the fact that the intervention was no more than an exploratory laparotomy or an enterostomy. The best therapy for this type of obstruction is conservative—diet, enemas and above all the administration of fluids and minerals. At the beginning of the discussion on functional ileus I emphasized that precise knowledge regarding intestinal innervation is very meager. I wish to state that even though I have classified the obstructions in cases of uremia, of lead poisoning, of coronary disease, of infection due to intestinal parasites, of acute alcoholism, of tabes and of hysteria, I do not know whether a relation exists between these conditions and the obstruction. All I wish to state is that an obstruction manifested itself in subjects affected with these diseases, and in view of the fact that no cause for the obstruction could be found I feel that it is wise to treat the obstruction in a symptomatic manner concomitantly with the disease itself. Since treatment of the general cause favorably influences the

obstruction, it is possible that there is a relation between the general disease and the obstruction. In any event, the relation is uncertain.

This is obviously not the case in functional ileus associated with peritonitis. It is probable that the peritoneal infection itself is capable of causing intestinal paralysis by action on the nerves and plexuses. Again, peritonitis acts directly on the muscle fibers of the intestine. The study of the muscular layers of the bowel in cases of peritonitis discloses considerable edema of the muscular fibers and of the tissues between the fibers as a result of the infection or of the hyperemia of the bowel. Surgical treatment in these cases should be regarded in various aspects. The principle of the treatment is to drain the peritoneal cavity. If this proves inefficient, one has to resort to enterostomy; the opening may close spontaneously or may have to be closed after recovery. In all of the cases this treatment can be efficiently supported by massive rehydration and remineralization.

POSTOPERATIVE ILEUS

This is a particular form of ileus, either paralytic or spastic, which may follow any operative intervention but most frequently follows an abdominal operation. This should not be confounded with postoperative ileus with obstruction which follows an abdominal operation. The latter is also of a paralytic nature but depends on a more or less severe peritoneal reaction; it belongs in the domain of the functional obstruction consecutive on peritonitis. I am speaking here of a postoperative ileus without any sign of peritoneal reaction. The cause of this condition is unknown, and for its treatment I have used lavage of the stomach, duodenal suction, hot applications to the abdomen and warm and cold enemas. The most satisfactory procedure is lavage of the stomach; the rest of the procedures gave favorable results in some of the cases but in others the results were uncertain. One can employ pharmaceutic products. I have experimented with many preparations, none of which proved very satisfactory regardless of whether their action was based on experimental or on clinical experience. Included in this group were posterior pituitary extract, peristaltin (a glucoside of Cascara sagrada), acetylcholine, physostigmine, atropine, opium and numerous other commercial preparations. In some of the cases this treatment was followed by the passage of gases and feces, but in the majority of cases the drug proved inefficacious, so that the actual effectiveness of these products remained problematic. As a result of experimental work, morphine has been employed in recent years to reestablish the intestinal peristalsis. In my experience this therapy has not given the results which were expected of it.

Intravenous Injections of Hypertonic Solutions.—Postoperative ileus is sometimes treated with injections of hypertonic solutions. From 10 to 20 per cent solutions of sodium chloride are most frequently employed. Introduced into a vein in a dose of 20 cc., such a solution will provoke a violent peristalsis and will relieve postoperative paralysis. Delrez and Orban have found this method inefficient in 66 per cent of cases of postoperative ileus, and these figures are confirmed every day. It is certain that the injection of a 20 per cent solution of sodium chloride may sometimes rapidly relieve the paralysis of the intestine and be followed by evacuation of feces and gases in a short while, but the untoward phases of this treatment are numerous and I feel that it is not the ideal treatment of postoperative ileus. Other hypertonic solutions were tried in man and the animal (sodium citrate, urea and dextrose) with results comparable to those obtained with hypertonic solution of sodium chloride. I emphasize once more that intravenous injection of hypertonic solution of sodium chloride should not be employed in cases of mechanical obstruction. Four years ago I stated that this treatment is not efficacious and is, in fact, dangerous, and only recently Aird expressed the same view. Some clinicians resort to the employment of enemas of a 20 per cent solution of sodium chloride in cases of paralytic ileus. I have not had any experience with this method, but I feel that it is probably not superior to those I have mentioned.

Spinal Anesthesia.—Leriche appears to be the first to have advised spinal anesthesia for the treatment of paralytic ileus (1912). Since then the method has been rapidly popularized. Wagner, Bonniot and Bartlett gave different explanations of its action, but these are incomplete and inadequate. Numerous publications emanating from the Surgical Society of Paris in 1927 make this method appear well founded, and I have observed that patients have a prompt evacuation a few minutes after the injection of a spinal anesthetic. However such a result is not always attained, and the method may result in regrettable accidents, as pointed out by Leriche himself. It is preferable, therefore, to use caution in employing spinal anesthesia for the relief of the paralytic postoperative obstruction and not to expect too brilliant results.

CONCLUSION

All the methods which I have mentioned for the treatment of postoperative ileus can be employed for any paralytic ileus. I feel, however, that some of them should not be used if the intestinal paralysis is due to an inflammatory peritoneal reaction. The aim of these methods is to provoke intestinal peristalsis, but since the peritoneal exudate should not be spread, I feel that it is best in cases of peritonitis to keep the bowel at rest.

In conclusion, I wish to say a few words about the therapy I regard as the most effective against postoperative ileus. In the greater number of cases this complication develops in a patient who previous to the operation was already in a state of dehydration and demineralization as a result of the malady which indicated the operation (vomiting, withholding of food, profuse sweating and diarrhea), or a similar state of dehydration and demineralization develops after an operation, owing to causes comparable to those just mentioned, to which should be added evaporation and hemorrhage during the operation. To sum up, postoperative ileus is produced as a result of loss of water and minerals, and the best means of preventing this complication consists in administering a satisfactory supply of fluids and minerals after surgical intervention. This is a most important preventive aspect of the problem. If despite everything postoperative ileus ensues, the best treatment is that of supplying massive doses of fluids and minerals. I believe that this furnishes a satisfactory explanation for the good results obtained by Dubois de Genève by blood transfusion in cases of postoperative ileus. It amounts to no more than a special form of supplying of water and minerals with its active antitoxic effects. Of all the therapeutic measures in the treatment of intestinal obstruction, rehydration and remineralization give the most satisfactory results. In certain exceptional cases all the means which were employed failed. In such cases one must employ a method, unpleasant though it may be, which may save a few lives, and perform an enterostomy, the effect of which is comparable to that which I have mentioned in cases of obstructions due to adhesions.

SPREADING PERITONITIS COMPLICATING ACUTE PERFORATIVE APPENDICITIS

EXPERIMENTAL STUDIES

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PHILADELPHIA

Approximately 300,000 persons in the United States will be operated on this year for acute appendicitis and its complications. Twenty thousand of these will die at an average age of 27 years. Fewer than 2,000 will die of acute appendicitis. More than 17,000 will die of peritonitis.

Of the 300,000 persons operated on, nearly 195,000 will have an intact appendix; the serous coat will be unruptured. The mortality will be less than 1 per cent. Of the 300,000, it is estimated that 105,000 will have peritonitis at the time of their admission to the hospital and approximately 1 of every 6 of these will die; 63,000 will have local peritonitis and approximately 3 per cent, or 1 in 30, will die; 42,000 will have spreading peritonitis and more than 15,000, or 1 in every 3, will die. Over 80 per cent of those who die will die of spreading peritonitis.

During the past six years our attention in the Department of Surgical Research, Temple University Medical School, has been focused on spreading peritonitis complicating acute perforative appendicitis. We have produced in dogs a form of spreading peritonitis which clinically, pathologically and from a bacteriologic and serologic point of view, closely resembles that seen clinically following acute perforative appendicitis. The bacteriologic findings are reported separately elsewhere.

INDUCTION OF SPREADING PERITONITIS IN DOGS

Selection of Animals.—The dogs were selected at random, except that the control dogs and the treated dogs were of approximately equal size and weight. Pregnant animals and animals weighing less than 4.5 Kg. were not used. No effort was made to prepare the dogs except that they were not fed on the morning of the operation.

Operative Technic.—The operation was performed with the dog under ether anesthesia. The abdomen was shaved, scrubbed with ether and painted with a 3.5 per cent tincture of iodine. Strict aseptic precautions were observed. A

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right rectus incision about 10 cm. long was made; the appendix was located, drawn up and dissected free of its mesenteric attachments, and all bleeding vessels were clamped and separately ligated with fine silk. A double ligature of silk was then tied tightly about the appendix as close to its base as possible. After inspection to make sure that hemostasis was complete, the abdominal contents were replaced and the wound was closed in layers, silk being used throughout. The fascia was reenforced with interrupted sutures. Drains were not used. During the operation precautions were taken to prevent the escape of blood into the peritoneal cavity. No dressing was applied.

Administration of Laxatives.—Early in the investigation it was found that by giving 30 cc. of castor oil to the average dog twenty-four hours after separating the appendix from its mesentery and ligating the blood vessels and the appendix at its base it is possible to induce spreading peritonitis. Table 1 shows that the mortality in this series of experiments was 68.52 per cent. Ninety-one and nine-tenths per cent of the deaths were caused by spreading peritonitis.

The next step was to give 30 cc. of castor oil to a group of animals directly after the operation. The mortality rose to 78.28 per cent, and 94.45 per cent of the dogs died of spreading peritonitis (control group *B*). An average dose of 54.1 cc. of castor oil was then administered to a third group of dogs directly after the operation. The mortality rose to 91.87 per cent, and 100 per cent died of spreading peritonitis (control group *C*).

Comment.—The results in control groups *A* and *B* prove that the time of administration influences the outcome, and the results in control group *C* show that the quantity of laxative administered also influences the outcome. Every animal that died after receiving 2 ounces of castor oil following the operation died of spreading peritonitis.

Postoperative Care.—The dogs were placed in metabolic cages and allowed to recover before being returned to the animal house. Food and water were placed before them. They were disturbed only when brought to the operating room for the administration of laxatives or for other treatment. They were returned to the animal rooms as rapidly as possible, with as little handling as possible. Special care was taken not to squeeze or massage the abdomen.

In the animal rooms no special precautions were taken except that the dogs were kept segregated in individual cages. The rooms were heated during the coldest weather only, the room temperature never being higher than 50 F. except when the weather made it so.

Postmortem examinations were carried out in all instances as soon as possible after death. If an autopsy was not performed to determine the cause of death, if the animal died of pneumonia or of some other complication within ten days, or if at a subsequent operation the appendix was found to be intact, showing that the ligature had slipped, the animal was discarded.

TREATMENT OF SPREADING PERITONITIS IN DOGS

Although 323 dogs were used, 58 of this number are not included in the control or treatment groups. The normal postoperative recovery

period of 18 of the 58 dogs was interrupted by another operation to obtain material for bacteriologic and histologic examinations. A number of these dogs recovered and were used subsequently as donors for blood transfusions and as donors of convalescent serum.

Thirteen animals died of the effects of the anesthetic before, during or immediately after the operation. Most of these deaths occurred in the early stages of the work. In 14 animals the ligature placed around the base of the appendix was not drawn sufficiently tight and became loose directly after the operation, or the mesentery was not completely separated from the appendix and gangrene of the appendix did not develop. Subsequent exploration of the abdomen in each instance revealed a normal appendix with no evidence of local or spreading peritonitis. Eleven animals were excluded because of delay in carrying

TABLE 1.—*Results of Administration of Castor Oil*

Control Group	Number of Dogs	Average Weight, Kg.	Laxative (Castor Oil), Cc.	When Given	Lived	Died	Mortality, Percentage	Average Duration of Life of Dogs That Died, Hr.	Pathologic Picture*	
									S. P.	L. P.
A	54	9.5	30	24 hr. after operation	17	37	68.52	67.24	91.90	8.10
B	23	9.26	30	Immediately after operation	5	18	78.28	61.95	94.45	5.55
C	12	9.4	54.1	Immediately after operation	1	11	91.67	66.00	100.00	0.00
Summary	89	9.38			23	66	74.16	65.35	93.93	8.07

* In this table and in the following ones S. P. indicates spreading peritonitis; L. P., local peritonitis.

out postoperative treatment or because of accidents. One dog died of hemorrhage, and in 1 case autopsy was incomplete.

Of the 265 dogs used, 158 received treatment for spreading peritonitis. Eighty-nine were used as controls and 18 for bacteriologic and histologic investigations. Control groups are designated A, B and C. Treatment groups are numbered 1, 2, 3, 4, 5, 6, 7, 8 and 9.

As the results of our bacteriologic investigations indicated the presence of anaerobes and especially of Clostridium welchii, it was decided to use Bacillus perfringens antitoxin in the treatment of induced spreading peritonitis in dogs, and our attention was directed toward determining the optimum dose and time of administration.

In treatment group 1, the administration of moderate doses of B. perfringens antitoxin intramuscularly reduced the mortality from 68.52 per cent (control group *A*) to 36.36 per cent. By increasing by 80 per cent the amount of laxative administered, the mortality was increased to 91.67 per cent (control group *C*); but this mortality was reduced in a group similarly prepared to 28.66 per cent —a decrease in the mortality percentage of 85.01 and a reduction in mortality of 70.9 per cent—by an improvement in the method of administration of the antitoxin (treatment group 2).

The question arose whether or not the intravenous injection of antitoxin would further reduce the mortality. To determine this, the antitoxin was given to a group of dogs prepared similarly to control group *B*. In this group, the animals, after having had the mesentery separated from the appendix and the base of the appendix ligated, received 30 cc. of castor oil directly after the operation. In the control group the mortality was 78.26 per cent; in the treatment group, after the intravenous injection of B. perfringens antitoxin, the mortality was reduced to 63.16 per cent—a decrease in the mortality percentage of 15.12 and a reduction in mortality of 19.3 per cent (treatment group 3).

COMMENT ON THE DOSE OF B. PERFRINGENS ANTITOXIN

Table 2 shows the amounts of B. perfringens antitoxin given intramuscularly per kilogram of body weight, together with the mortality and the average postoperative duration of life of the dogs that died.

TABLE 2.—*Results of Administration of B. Perfringens Antitoxin in the Treatment of Spreading Peritonitis*

Treatment Group	Number of Dogs	Average Weight, Kg.	Laxative (Castor Oil), Cc.	When Given, Hr. After Operation	Antitoxin, Cc.	Average Dose per Kg., Cc.	Lived	Died	Mortality, Percentage	Average Duration of Life of Dogs That Died, Hr.	Pathologic Picture S. P.	Pathologic Picture L. P.
1	44	8.74	30.00	24	28.43	3.35	28	16	36.36	88.56	77.72	27.28
2	15	9.40	57.66	24	29.10	3.10	11	4	26.66	118.00	50.00	50.00
Summary of intramuscular antitoxin groups	59	8.90	.....	..	26.60	3.21	39	20	33.90	.....	.....	.....
Treatment group 3 (antitoxin, intravenous)	19	8.50	30.00	Immediately	42.10	4.95	7	12	63.16	76.00	83.33	16.67

Group 1 is made up of the dogs that first received antitoxin. The amount given was small, moreover, as 43.18 per cent of the dogs received only one dose, 3.64 per cent received two doses and 43.18 per cent received three doses. The dogs that recovered received an average amount larger by 77 per cent than the dose given those that died. The average postoperative duration of life of the dogs that died in group 3 was eighty-eight and one-half hours. No death occurred in less than forty-eight hours. Nine of the 16 dogs that died could have received a second dose and 5 a third dose of antitoxin. The dose of antitoxin in cubic centimeters per kilogram was slightly larger for group 1 than for group 2. In group 2, both the dogs that survived and those that died received approximately the same amount of antitoxin.

From the standpoint of mortality and the lengthened duration of life of the dogs that died after the operation, the results in group 2 are

remarkable, especially when it is realized that the dogs in this group received doses of laxative averaging 89 per cent larger than those given to group 1.

At this point in our investigation the question was raised how much, if any, of the reduction of mortality achieved by the use of B. perfringens antitoxin was due to the antibodies present in normal horse serum, the vehicle for the Cl. welchii antitoxin. To determine this, a group of 20 dogs (treatment group 4) was treated with normal horse serum injected intramuscularly, spreading peritonitis having been induced in the manner previously described. At this point it may be stated, to avoid repetition, that the operative technic was precisely the same for all dogs in both control and treatment groups, the only variable factor being the time of administration and the amount of castor oil given.

The results obtained with horse serum are shown in table 3.

TABLE 3.—*Experimental Group 4—Horse Serum*

Number of Dogs	Average Weight, Kg.	Laxative (Castor Oil), Cc.	Horse Serum, Cc. (Average)	Lived	Died	Mortality, Percentage	Average Duration of Life of Dogs That Died, Hr.	Pathologic Picture	
								S. P.	L. P.
20	9.63	37.5	27.3	8	12	60	80.3	91.67	8.33

The administration of horse serum reduced the mortality 12.43 per cent and increased by nearly thirteen hours the average duration of life of the dogs that died after the operation. The percentage of dogs that died from spreading peritonitis was increased 1.4 per cent.

Since B. perfringens antitoxin seemed to control satisfactorily the toxemia produced by Cl. welchii, we felt it might be advantageous to combine other antiserums or whole blood with the antitoxin in order to control the effects of other organisms, especially of Bacillus coli and of Streptococcus.

Before instituting the combined treatments for spreading peritonitis, we decided to determine the effect of whole blood alone, given intravenously.

Each of a group of 18 dogs was given a total average dose of 179.83 cc. of whole blood (not immunized); approximately 60 cc. was given on the day of the operation and the same amount on the second and third days after the operation. The mortality in this group (treatment group 5) was 91.66 per cent, and the average postoperative duration of life of the dogs that died was sixty-three hours. In treatment group 6, injections both of whole blood and of B. perfringens antitoxin were given. As the average weight of the dogs used in this experiment was greater the amount of blood was increased accordingly,

each dog receiving a total average dose of 206 cc. on consecutive days. The dose of perfringens antitoxin injected was 4.83 cc. per kilogram of body weight. The mortality in this group was 33.33 per cent; the average postoperative duration of life of the dogs that died was sixty-seven and one-half hours. The results in the experiments on dogs of these two groups are summarized in table 4.

In both these groups the laxative was administered immediately after the operation.

The dogs in treatment group 7 received immune serum in addition to B. perfringens antitoxin. This serum was obtained from dogs that had received antitoxin and had recovered from induced spreading peritonitis following rupture and gangrene of the appendix. The dose of antitoxin injected was 4 cc., and

TABLE 4.—*Treatment Groups 5 and 6—Transfusions*

Treatment Group	Number of Dogs	Average Weight, Kg.	Treatment: Laxative (Castor Oil), Cc.	Treatment: B. Perf. Ant., Cc.	Treatment: Whole Blood, Cc.	Lived	Died	Mortality, Percentage	Average Duration of Life of Dogs That Died, Hr.	Pathologic Picture: S. P.	Pathologic Picture: L. P.
5	12	9.46	30	0	179.83	1	11	91.66	63.12	91	9
6	12	11.18	30	54	206.00	8	4	33.33	67.50	100	0

TABLE 5—*Treatment Groups 7, 8 and 9*

Treatment Group	Number of Dogs	Average Weight, Kg.	Laxative (Castor Oil), Cc.	B. Perf. Ant., Cc.	Additional Cc.	Lived	Died	Mortality, Percentage	Average Duration of Life of Dogs That Died, Hr.	Pathologic Picture: S. P.	Pathologic Picture: L. P.
7	12	14.17	30	56.66	Immune blood serum 52.17	8	4	33.33	96	100	0
8	12	11.11	30	24.66	Polyvalent B. coli serum 24.66	8	4	33.33	72	100	0
9	12	9.35	30	0	Immune blood serum, lyophilized 70	9	3	25.00	48	100	0

that of immune serum 3.72 cc., per kilogram of body weight. The mortality in this group was 33.33 per cent, but the average postoperative duration of life of the dogs that died was increased to ninety-six hours, which is longer than any of the treated dogs lived except those in group 2.

The dogs in treatment group 8 received polyvalent B. coli serum in addition to B. perfringens antitoxin. The dose of antitoxin was 2.18 cc., per kilogram of body weight. The mortality was 33.33 per cent, and the average postoperative duration of life of the dogs that died was seventy-two hours.

The dogs in treatment group 9 received lyophilized immune blood serum given intramuscularly. The average amount given to each animal was 70 cc. per kilogram of body weight. The mortality was 25 per cent; the average postoperative duration of life of the dogs that died was forty-eight hours (table 5).

The dogs in all these groups received the laxative immediately after operation.

COMPARISON OF RESULTS OBTAINED IN DIFFERENT GROUPS OF ANIMALS

The difference in the average weights of dogs in the two groups, 0.15 Kg., is a negligible factor. The average dose of castor oil given to the treatment groups exceeded that given the control groups by 1.22 cc. While this is a small average increase, in the aggregate it amounts to 129.32 cc., and any effect it might have would be unfavorable to the survival of the dogs in the treatment group, because of the greater likelihood of increased peristalsis, which makes localization more difficult. The postmortem examinations which were made in over 95 per cent of

TABLE 6.—*Comparison of the Results Obtained in the Control Groups and the Different Treatment Groups*

Groups	Number of Dogs	Mortality, Percentage	Average Duration of Life of Dogs That Died, Hr.	Pathologic Picture: Spreading Peritonitis
Control groups, A, B, C	89	74.16	65.35	93.93
Treatment groups 1 and 2, B. perfringens antitoxin (intramuscularly)	59	33.89	94.40	66.67
Treatment group 3, B. perfringens antitoxin (intravenously)	19	63.16	76.00	83.33
Treatment group 4, horse serum	20	60.00	80.30	91.67
Treatment group 5, blood transfusion	12	91.66	63.12	91.67
Treatment group 6, B. perfringens antitoxin and whole blood	12	33.33	67.50	100.00
Treatment group 7, B. perfringens antitoxin and immune serum	12	33.33	96.00	100.00
Treatment group 8, B. perfringens antitoxin and B. coli serum	12	33.33	72.00	100.00
Treatment group 9, immune blood serum, lyophilized	12	25.00	48.00	100.00

Combined Mortality of All Treatment Groups except 3, 4 and 5

Number of Dogs	Lived	Died	Mortality, Percentage
107	72	35	33.64

instances showed that the lowered mortality in the treatment group was due to a greater tendency to localization of the process. This is corroborated not only by the lower mortality (74.16 per cent as compared to 39.59 per cent in the control group) but also by the increase in the average number of hours of survival of dogs that died after the operation (nineteen hours, an increase of 29.02 per cent) (table 6).

At subsequent operations on the dogs that recovered the gross findings showed that in the control group the appendix was completely absorbed in 60 per cent of instances and partially absorbed in 40 per cent. In the treatment group, 23 of the dogs were still living when this report was made, and with 8 others notations were not made at the time of the operation.

SUMMARY OF THE TREATMENT OF LAXATIVE-INDUCED SPREADING PERITONITIS IN DOGS

The mortality from laxative-induced spreading peritonitis in non-treated control groups A, B, and C was 74.16 per cent.

The mortality from laxative-induced spreading peritonitis in dogs treated with horse serum given intramuscularly was 60 per cent.

The mortality from laxative-induced spreading peritonitis in dogs treated with B. perfringens antitoxin alone was 41.03 per cent.

The mortality from laxative-induced spreading peritonitis in dogs treated with B. perfringens antitoxin given intravenously was 63.16 per cent.

TABLE 7.—*Comparison Between the Control and Treatment Groups*

	Number of Dogs	Average Weight, Kg.	Average Weight, Kg.		Average Dose Castor Oil, Cc.	Treatment		
			Lived	Died				
Control groups.....	89	9.73	9.27	9.90	33.26			
Treatment—B. perfringens antitoxin alone and combined with whole blood, Bacillus coli serum, and immune blood serum	114	9.95	10.88	10.28	24.38	B. Perfringens Antitoxin		
						Average Dose, Cc.	Lived	Died
						36.1	37.4	34.02

	Number		Mortality, Percentage	Pathologic Picture		Average Duration of Life of Dogs That Died, Hr.	Subsequent Examination at Operation		
	Lived	Died		S. P.	L. P.		A. A.*	L. P.	Autopsy
Control groups	23	66	74.1	93.9	6.07	65.92	60.0	40.0	5
Treatment—B. perfringens antitoxin alone and combined with whole blood, Bacillus coli serum, and immune blood serum	70	44	38.5	72.7	18.9	85.02	60.9	39.1	0

* Acute appendicitis.

The mortality from laxative-induced spreading peritonitis in dogs treated with B. perfringens antitoxin given intramuscularly was 33.68 per cent.

The mortality from laxative-induced spreading peritonitis in dogs treated with blood transfusions alone was 91.66 per cent.

The mortality from laxative-induced spreading peritonitis in dogs treated with blood transfusion and B. perfringens antitoxin given intramuscularly was 33.33 per cent.

The mortality from laxative-induced spreading peritonitis in dogs treated with immune blood serum and B. perfringens antitoxin was 33.33 per cent.

The mortality from laxative-induced spreading peritonitis in dogs treated with B. perfringens antitoxin combined with polyvalent B. coli antitoxin was 33.33 per cent.

The mortality from laxative-induced spreading peritonitis in dogs treated with lyophilized immune serum alone was 25 per cent.

. . . . . .

The maximum mortality in the control groups was in control group C—91.87 per cent.

The maximum mortality in the treatment groups was in treatment group 5—91.66 per cent.

The minimum mortality in the groups treated with B. perfringens antitoxin was in treatment group 3—26.68 per cent.

The minimum mortality in all treatment groups was in treatment group 9—25 per cent.

. . . . . .

The average postoperative duration of life of the dogs that died in the control group was sixty-six hours.

The average postoperative duration of life of the dogs that died in the treatment group was eighty-five hours.

The maximum postoperative duration of life of the dogs that died in the control groups was in group A—sixty-eight hours.

The maximum postoperative duration of life of the dogs that died in the treatment groups was in group 3—one hundred and eighteen hours.

The minimum postoperative duration of life of the dogs that died in the control groups was in group B—sixty-two hours.

The minimum postoperative duration of life of the dogs that died in the treatment groups was in group 9—forty-eight hours.

The average percentage of animals dying from spreading peritonitis, in control groups A, B and C was 94 per cent.

The average percentage of animals dying from spreading peritonitis, in treatment groups 1, 2 and 3, which were treated with B. perfringens antitoxin alone, was 50 per cent.

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DEGENERATION OF INFUNDIBULAR NERVE FIBERS IN THE CAT WITHOUT APPRECIABLE POLYDIPSIA

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The denervation theory of the causation of diabetes insipidus holds high interest at the present time. This theory is based on the assumption that diabetes insipidus is due to the absence of, or to a deficiency in, the antidiuretic principle which is elaborated by hypophysial tissue. It depicts that this tissue is activated only by neurogenic influences carried by the nerve fibers which take origin in the hypothalamus and pass to the hypophysis by way of the infundibular stalk.

In an early statement of the theory, the antidiuretic principle was assumed to be elaborated by the epithelial investment of the pars nervosa, namely, by both the pars intermedius and the pars tuberalis.[1] Later, attention was focused on the infundibular process (the enlarged distal portion of the pars nervosa) as the secretory structure. This shift was largely due to the successful extraction of the antidiuretic principle from the neural lobes of birds and whales, which are free from any epithelial investment,[2] and also to the recognition of anatomic changes in the infundibular process in the cat following hypothalamic lesions which, in turn, were associated with diabetes insipidus.[3] The successful occlusion of the hypophysial stalk in the monkey without elicitation of diabetes insipidus [4] resulted in the focusing of attention

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1. Cushing, H.: Papers Relating to the Pituitary Body, Hypothalamus and the Parasympathetic Nervous System, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 31.

2. Geiling, E. M. K.: Bull. Johns Hopkins Hosp. **57**:123, 1935.

3. (*a*) Fisher, C.; Ingram, W. R.; Hare, W. K., and Ranson, S. W.: Anat. Rec. **63**:29, 1935. (*b*) Fisher, C.; Ingram, W. R., and Ranson, S. W.: The Relation of the Hypothalamico-Hypophyseal System to Diabetes Insipidus, Arch. Neurol. & Psychiat. **34**:124 (July) 1935. (*c*) Fisher, C., and Ingram, W. R.: Endocrinology **20**:762, 1936.

4. Mahoney, W., and Sheehan, D.: Brain **59**:61, 1936.

on the entire pars nervosa [5] as the source of the antidiuretic principle; i. e., the infundibulum as well as the infundibular process.

Except for this change in the hypophysial structure suspected as the secretory tissue, the fundamental denervation hypothesis has remained unchanged—namely, that the elaboration of the antidiuretic principle is dependent on intact hypothalamic innervation. If this is true, complete degeneration of the infundibular nerve fibers should invariably result in the appearance of diabetes insipidus in its maximal form, because the antidiuretic principle would be completely lacking. One would expect the magnitude of the polydipsia per kilogram of body weight to be fairly consistent in a given species and probably from one species to another. Further, in the instance of nearly complete denervation there should be some correlation between the degree of denervation and the severity of the diabetes insipidus.

Several experimental studies are now on record which establish the fact that lesions occurring in the ventral hypothalamus frequently precipitate diabetes insipidus.[6] Most of the experiments in these series have not been sufficiently controlled anatomically for any attempt at a positive correlation between the occurrence or severity of diabetes insipidus and the extent of degeneration of the infundibular nerve fibers. Fisher and Ingram and their associates have reported such a correlation in their sizable series of experiments on cats and have interpreted their results as supporting rather conclusively the denervation theory. Analysis of their published data gives one the impression that there was considerable variation in the water intake per kilogram of body weight (body weight was stated only infrequently) present in the preparations which they considered totally denervated (ventral infundibulum only). Certainly the maximum fluid intake per unit of body weight encountered by them in experiments on the cat is far below that on record for experiments on the rat and the dog. Richter reported that certain of his rats drank their own weight of water in twenty-four hours. A water intake of 600 to 900 cc. per kilogram per day is not unusual for the diabetic dog. We have encountered an instance of a water intake of 1,300 cc. per kilogram per day for a dog weighing 5.3 Kg. This was in the presence of a high food intake. Taking into account the range in weight of cats, the maximal water intake encountered by Fisher and Ingram for the cat could not

5. Ingram, W. R., and Fisher, C.: Anat. Rec. **66**:271, 1936.

6. (*a*) Camus, J., and Roussy, G.: Compt. rend. Soc. de biol. **83**:764, 1920. (*b*) Houssay, B. A.; Carulla, J. E., and Romana, L.: ibid. **83**:1250, 1920. (*c*) Bailey, P., and Bremer, F.: Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773 (Dec.) 1921. (*d*) Curtis, G. M.: The Production of Experimental Diabetes Insipidus, ibid. **34**:801 (Dec.) 1924. (*e*) Richter, C. P.: Brain **53**:76, 1930.

have been over 250 or 300 cc. per kilogram of body weight, and in most instances it was considerably less. Fisher [7] informed me that he feels that the water exchange in the cat is below that in the rat and the dog and that he and his associates did encounter maximal diabetes insipidus for the cat in certain of their animals.[7]

MATERIAL AND METHOD

Cats in good physical condition were used, which in most cases had been conditioned to our cage regimen. Water was continually available to them during a twenty-three hour period daily. Food, which consisted of a mixture of half a prepared dog food and half salmon, was available in their cages for sixteen hours daily. The water drunk and the food eaten were measured every twenty-four hours. In some cases during the immediate postoperative period limited milk was given. In these instances the milk was included in graphing fluid intake. In graphing fluid and food intake on the basis of kilogram of body weight, the weight of the animal at operation was used throughout for the basis of calculation. No routine quantitative urinary studies were made. The absence of polydipsia is an adequate criterion for the absence of diabetes insipidus. In addition, we are convinced on the basis of observations in our laboratory that the severity of diabetes insipidus is most reliably measured by the magnitude of the polydipsia.

Operative Procedure.—The ventral portion of the hypothalamus was exposed on one side by the usual intracranial subtemporal approach. Then by means of subpial manipulation in the ventral hypothalamus with a small, blunt probe, an attempt was made to isolate the entire hypophysis from the hypothalamus, thus sectioning the nerve fibers before their entrance into the infundibulum. The whole procedure is easily accomplished with good visibility and with complete hemostasis. The greatest difficulty encountered was in sectioning those fibers which leave the hypothalamus and enter the infundibulum at its anterior extremity. We have now learned to do this with certainty by running the probe anteriorly between the pia and the surface of the hypothalamus and making the lesion by inward traction into the hypothalamus rather than by our former method of outward traction after protruding the probe into the hypothalamic tissue at the level of the infundibulum.

HISTOLOGIC STRUCTURE

The location and extent of the lesion as well as the extent of degeneration of the infundibular nerve fibers were determined at the termination of the experiment by sectioning the hypothalamus-hypophysis block (fixation in solution of formaldehyde and embedding in paraffin) longitudinally and mounting three sets of consecutive sections (every tenth or fifth section). One set was stained for cells with cresyl violet, another for nerve fibers by a modification of the Pal-Weigert method, and the third for nerve fibers by the method of Bodian.[8] Complete demarcation of the hypophysis from the hypothalamus by scar tissue, as illustrated in figure 1, is sufficient evidence of complete degeneration of the infundibular nerve fibers. Nevertheless, the silver preparations, as illustrated in figure 2, were indispensable in doubtful instances of complete isolation.

We found that the Bodian method was not only reliable but admirable for this study, because of the fact that the cellular elements show up so well

7. Fisher, C.: Personal communication to the authors.

8. Bodian, D.: Anat. Rec. **65**:1, 1936.

in relation to the nerve fibers. Figure 3 is a low power photomicrograph of a section of the hypophysis and ventral hypothalamus of the cat, stained by this method. Note that at this low power the distal half of the infundibulum shows as a compact nerve trunk; this appearance is produced by a concentration of the nerve fibers in this region. In addition, the various parts of the hypophysis as well as their lines of separation are readily identified. The condensation of the nerve fibers in the distal half of the infundibulum is no doubt due to the progressive decrease in the width and diameter of the infundibulum in going distally from the hypothalamus. This region of concentration of fibers in the infundibulum was therefore particularly scrutinized for nerve fibers in our serial preparations. It is this region of the ventral portion of the infundibulum that is illustrated in the high power photomicrographs in figure 2.

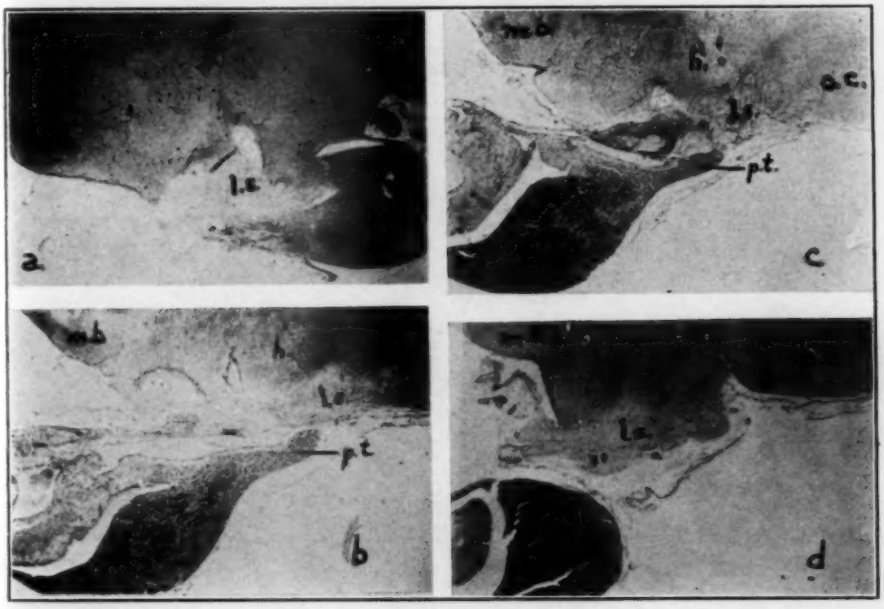

Fig. 1.—Low power photomicrographs of representative sections taken from the serial sections for cat 1, showing the location and extent of the hypothalamic lesion. Sections *a*, *b* and *d* were stained by the Bodian method; section *c* was stained with phosphotungstic acid. Sections *a* and *b* are sections to the left of the midline, and sections *d* and *c*, to the right. The abbrevations are: *m.b.*, mamillary body; *o.c.*, optic chiasm; *l.s.*, lesion scar; *h*, hypothalamus; *p.t.*, pars tuberalis.

The presence or absence of nerve fibers as well as the general size and number of cellular elements in the infundibular process is likewise somewhat indicative of the extent of degeneration of the infundibular nerve fibers. This fact is illustrated in figure 2

RESULTS

We operated on 29 cats, of which 7 either did not survive the operation long enough for adequate observation or were found dead at such a time that reliable anatomic studies could not be made. The daily food and water consumption of the remaining 22 cats was

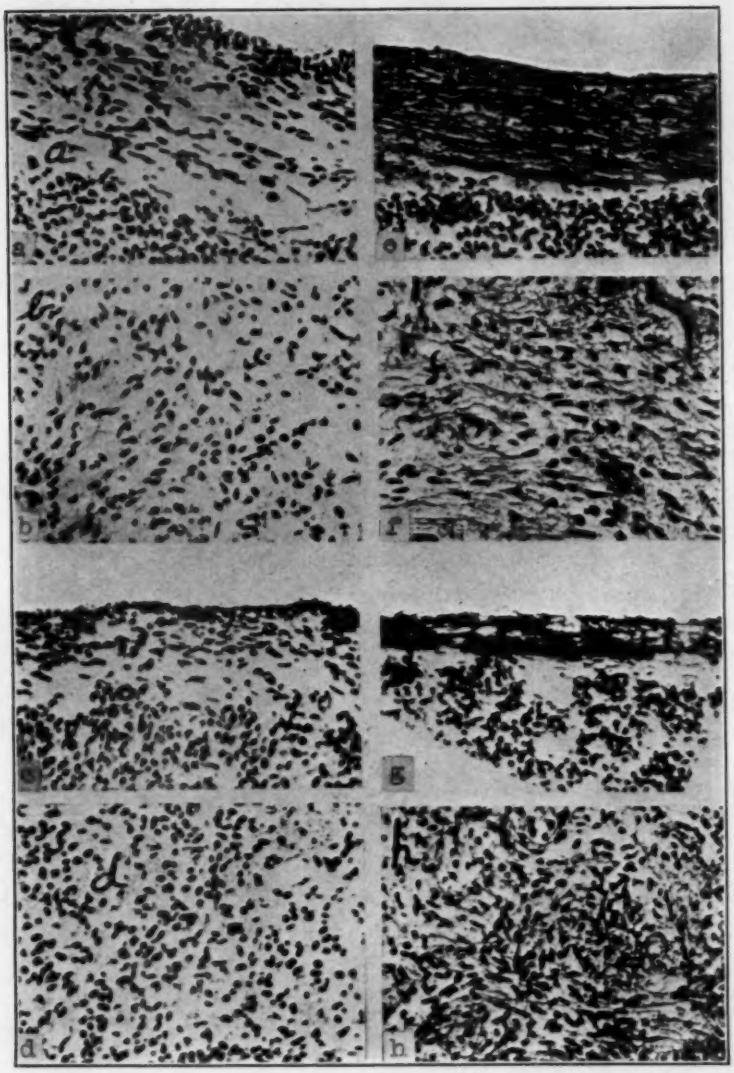

Fig. 2.—Representative high power photomicrographs, all of the same magnification, from sections stained by the Bodian method. Section *a* was taken from the distal region of the ventral infundibulum of cat 2 (as indicated by arrow 1 in figure 3). Compare with *c*, *e* and *g*. Note the absence of nerve fibers, the prominence of cellular elements and the absence of narrowing in the infundibulum. Section *b* was taken from the ventral and somewhat peripheral region of the infundibular process of cat 2 (as indicated by arrow 2 in figure 3). Compare with *d*, *f* and *h*. Note the absence of nerve fibers and the increased number of cellular elements as compared with the normal, shown in *f*. Section *c* (cat 3) is equivalent to sections *a*, *e* and *g*. Note that the width of the infundibulum is less and the cellularity greater than in *a*. Section *d* (cat 3) is equivalent to sections *b*, *f* and *h*. Section *e* was taken from the region of the ventral infundibulum of a normal cat (indicated by arrow 1 in figure 3). Note that the histologic picture of the entire width of the infundibulum at this point is essentially that of a compact nerve trunk. Section *f* was taken from the region of the infundibular process of a normal cat (indicated by arrow 2 and shown in figure 3). Section *g* (cat 4) is equivalent to sections *a*, *c* and *e*. Note that the infundibulum is much narrowed in spite of the presence of many nerve fibers. Section *h* (cat 4) is equivalent to sections *b*, *d* and *f*. Note the increased cellularity as compared with *f*, in spite of the presence of many nerve fibers.

observed over periods ranging from five weeks to five months. During the period of observation the cats remained in good health and exhibited no deviation from the normal in behavior except (for a few days) slight sluggishness and caution in using the jaws because of the soreness of the severed temporal muscle. As a rule their appetites continued normal or slightly enhanced directly after the operation, but in a few instances forced feeding (milk by stomach tube) was necessary for several days, after which spontaneous feeding was resumed. In no instance was there any indication of depressed function of the pars anterior as evidenced by hypoglycemic crises.

In most cases the experiments were terminated at the close of the period of observation of food and water consumption. After the

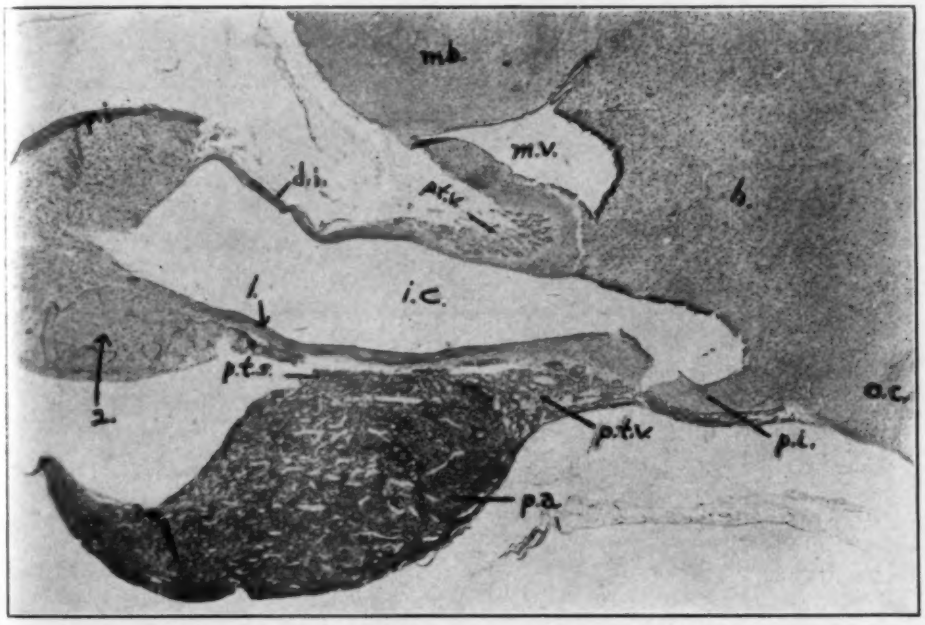

Fig. 3.—Low power photomicrograph of a longitudinal section through the hypothalamus and hypophysis stained by the Bodian method. The abbreviations are: *m.b.*, mamillary body; *h*, hypothalamus; *o.c.*, optic chiasm; *iii v.*, third ventricle; *i.c.*, infundibular cavity; *pi.*, proximal portion of the infundibulum; *p.t.v.*, pars tuberalis, vascular portion; *p.t.s.*, pars tuberalis solid portion; *p.a.*, pars anterior; *d.i.*, distal portion of the infundibulum. The letters *p.i.*, indicating the infundibular process, are incorrectly placed, but arrow 2 identifies this structure. Arrow 1 indicates the area shown magnified in figure 2 (*e*); arrow 2 indicates area shown magnified in figure 2 (*f*).

regimen of cage observation, one group of animals was placed in an outdoor breeding pen in connection with observations on reproduction (summer 1936). These animals became heavily infested with fleas,

and several deaths occurred before the cause of death was ascertained. The cats of this group included in the following report were found either in a state of collapse or shortly after death, so that adequate fixation of the brain tissue was obtained.

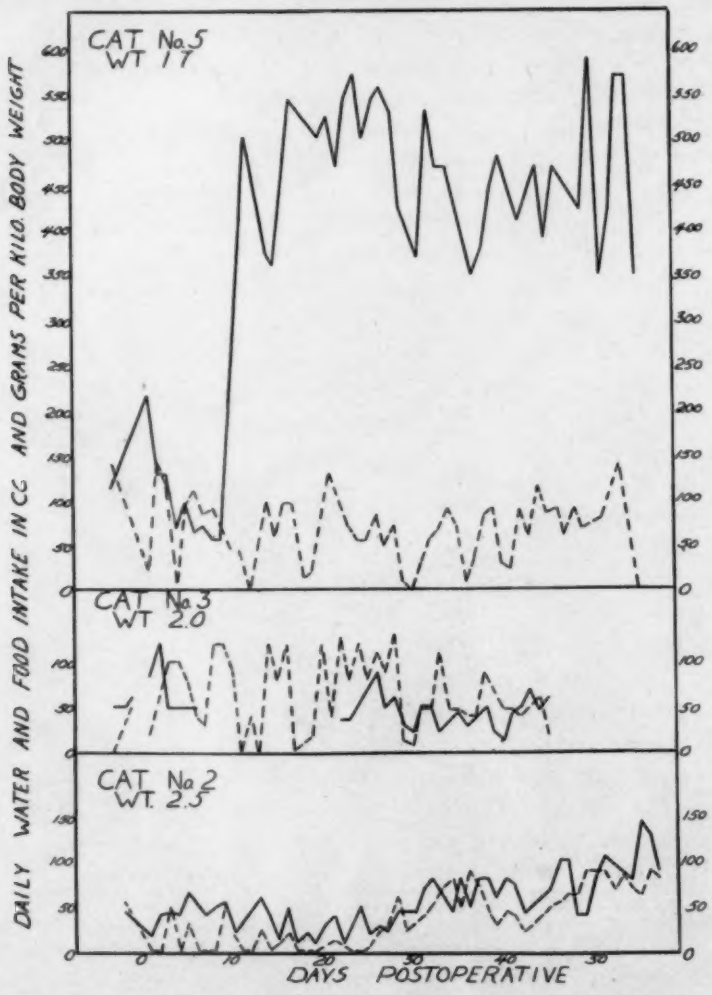

Fig. 4.—Food intake in grams and water intake in cubic centimeters.

Complete degeneration of the infundibular nerve fibers occurred in 9 of the 22 animals. The tissues of 3 of these preparations are illustrated in figures 1 and 2. Only 1 of these 9 animals had striking polydipsia; for 2 others there was a slight elevation in water consumption. The water consumption was normal or essentially so for the remaining 6 animals. The hypophysis was practically denervated in 7

additional animals, since only occasional nerve fibers remained in the pars nervosa. In some of the cases nerve fibers were present only in the posterior portion of the infundibulum, the anterior portion being devoid of fibers. Three of these 7 animals exhibited slight polydipsia, whereas the water consumption was normal or essentially so for the remaining 4. Severance of the infundibular nerve fibers was incomplete in the remaining 6 animals in the group of 22. A large number of nerve fibers were present throughout the extent of the pars nervosa. One of these animals exhibited a slightly enhanced water intake, whereas the others showed no deviation from the normal. The following description is typical of the series.

The daily food and water consumption of the only animal (cat 5) which exhibited striking polydipsia is graphed at the top of figure 4. Note the typical abrupt onset of the permanent phase of the polydipsia during which the water intake ranged from 350 to 575 cc. per kilogram of body weight per day. There was an accompanying polyuria of the same magnitude. The food consumption was normal or slightly enhanced. Subsequent to the period graphed, fifty-fourth day, this cat was placed outside in the breeding yard until the eightieth day, at which time it was again placed on record for a week's period. At this time the water intake remained consistently just above 300 cc. per kilogram of body weight per day. The cat was then returned to the breeding pen and was found in a state of collapse on the one hundred and second day after operation. At the time of operation the cat was in good physical condition, though tending to be lean. It weighed 1.7 Kg. at that time. Just previous to death it weighed 2.2 Kg. Much intra-abdominal fat was noted at autopsy. Good silver preparations were not obtained because of poor fixation and because the hypophysis had been largely separated from the hypothalamus in removal of the brain. The hypophysis had been completely isolated at the time of operation, because the Nissl and Weigert preparations revealed that the hypothalamic tissue below the fornix and caudal to the optic chiasm was involved by the lesion. There was no apparent macroscopic encroachment on the epithelial portion of the hypophysis.

The food and water consumption of cat 3 is graphed immediately beneath that of cat 5 in figure 4. Note that this cat's water consumption did not exceed the preoperative intake in spite of a definitely enhanced food intake. The water intake for a period following operation was not obtained because it was daily contaminated with urine and feces. This cat, as is evident from the record of food consumption, remained in good health throughout the period of observation and exhibited no deviation from the normal in behavior either immediately after operation or subsequently. It weighed 2 Kg. at the time of operation and 2.2 Kg. when killed. It was killed on the forty-ninth day after operation. The

entire ventral tip of the hypothalamus was involved by scar tissue. In addition, the needle path reached at the level of the caudal extent of the optic chiasm dorsally and anteriorly well above the dorsal level of the chiasm. There was some narrowing of the infundibular tissue as well as some central disappearance of the tissue of the infundibular process, so that the infundibular cavity extended slightly into this structure. There was a decided increase in number as well as a decrease in size of the cellular elements of both the infundibular process and the infundibulum. The whole of the pars nervosa was devoid of nerve fibers. Most of these features are readily appreciated in a comparison of the photographs of portions of the infundibulum and infundibular process shown in *c* and *d* in figure 2 with like photographs taken of normal tissue and shown in *e* and *f* in figure 2.

The food and water intake of cat 2 is graphed at the bottom of figure 4. This cat during the first three weeks after operation had a sluggish appetite, although it exhibited normal behavior in other respects. As the food consumption returned to normal or slightly above normal, the water consumption likewise rose above the preoperative level. This cat, therefore, exhibited a suspected trace of diabetes insipidus, although this is not at all certain in the presence of the high food intake. At the time of operation it weighed 2.5 Kg. During the time of sluggish appetite the weight dropped to 2 Kg. This loss was regained by the time the cat was killed, the sixtieth day after operation. The lesion involved only the extreme ventral portion of the hypothalamus; however, the hypophysis was entirely separated, as the whole of the pars nervosa was devoid of nerve fibers. The tissue of the infundibulum was not narrowed as in cat 4, but there was some central disappearance of the infundibular process. The whole of the pars nervosa exhibited an increase in the number and a decrease in the size of the cellular elements. Most of these features are illustrated in figure 2.

The location and extent of the lesion in cat 1 are illustrated in figure 1. It is readily evident that the hypophysis was entirely isolated from the hypothalamus by scar tissue involving the ventral portion of the hypothalamus. Note also that the lesion involved the hypothalamic tissue just posterior to the optic chiasm, so that it is certain that all fibers coming from the anterior hypothalamus were cut. The rather marked central disappearance of the tissue of the infundibular process is evident in a comparison of this structure, shown in *b* of figure 1, with that of the normal infundibular process, shown in figure 3. At the same time it is seen at this low power that there was no narrowing of the infundibular tissue. The fact that there was no macroscopic infringement on the pars anterior and only slight encroachment on the pars tuberalis is particularly illustrated in *c* of figure 1. This section

is stained with phosphotungstic acid, whereas sections *a*, *b* and *d* are stained by the Bodian method. This cat at operation weighed 1.6 Kg. and eighty-three days later weighed 1.85 Kg., having lost weight immediately after operation. In this instance, food and water consumption was recorded only periodically after the eighteenth day after operation. The average food and water intakes per kilogram of body weight were:

Third week after operation—food 55 Gm.; water 115 cc.
Sixth week after operation—food 115 Gm.; water 120 cc.
Tenth week after operation—food 125 Gm.; water 150 cc.

The graphed curves, therefore, were essentially the same as those for cat 2. It was listed in the statistical grouping as displaying slight polydipsia. The cat was in good health when last weighed, on the eighty-third day after operation, and was found dead on the eighty-eighth day after operation. A fair injection was obtained, so that the location and extent of the lesion as evident from figure 1 were determined adequately.

COMMENT

It is immediately apparent that in this series of experiments there was no correlation between the occurrence or the severity of polydipsia and the extent of degeneration of the infundibular nerve fibers. It is therefore doubtful that the polydipsia which follows certain hypothalamic lesions is primarily the result of sectioning either the whole or any part of the hypothalamicohypophysial system of nerve fibers. If the secretion of the antidiuretic principle were dependent on the intactness of these nerve fibers, we should have encountered a striking and consistent polydipsia (maximal for the cat) in each of the 9 animals in which they were completely degenerated. At the same time, the 7 animals in which essentially all of these fibers were eliminated should have exhibited a polydipsia somewhat near the maximal. The results obtained were in contrast to such an expectancy. A striking polydipsia was encountered with 1 animal only, namely, cat 5. In the other animals in which there was an increase or a suspected increase in water consumption, this increase was so slight as compared with that present in cat 5 that for purposes of analysis they all can be grouped with the animals in which no postoperative increase occurred.

The absence of polydipsia following degeneration of the infundibular nerve fibers in one instance alone is a positive demonstration of the fallacy of the denervation theory, provided the elaboration of the antidiuretic principle is confined to hypophysial structures and that no complicating factors entered into the experiment. We see one possible way in which these experiments may have been complicated; namely, we may have eliminated by our operative procedure the secretion of the

antidiuretic principle and, in addition, paralyzed the mechanism of the pars anterior which is essential for the occurrence of diabetes insipidus in its maximal form. There are several investigations which suggest that the pars anterior mediates its effect in this respect by way of its thyrotropic principle.[9] The thyroid glands of these animals appeared normal grossly but were unfortunately accidentally discarded before histologic studies were obtained. There was no outward evidence of hypothyroid function and no indication of depressed function of the pars anterior as evidenced by hypoglycemic crises. There was in no instance any macroscopic evidence of involvement of the pars anterior of the hypophysis. Nevertheless, the possibility of such a complication must be ruled out in another series of experiments designed to answer the question.[10]

It should be pointed out that, assuming that these experiments were not complicated as has been outlined, they do not necessarily eliminate the possibility that the pars nervosa may be a structure which elaborates the antidiuretic principle. There were healthy-looking cellular elements in the remaining tissue of the pars nervosa, which on the basis of their histologic structure might be suspected of a secretory function as readily as might the cellular elements in the normally innervated pars nervosa. Although there was a decided increase in the cellular elements of the pars nervosa following degeneration of the infundibular nerve fibers, the staining characteristics of the cells were not changed, as evidenced by cresyl violet preparations. This is illustrated in figure 3 of a previous paper.[10a] Again, the denervation concept might hold with reference to the pars nervosa if, perchance, the tissue of the hypothalamus possesses, in common with the pars nervosa, antidiuretic secretory powers.[11] We

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9. (*a*) Barnes, B. O.; Regan, J. F., and Bueno, J. G.: Am. J. Physiol. **105**:559, 1933. (*b*) Biasotti, A.: Compt. rend. Soc. de biol. **115**:329, 1934. (*c*) Mahoney, W., and Sheehan, D.: Am. J. Physiol. **112**:250, 1933. (*d*) Keller, A. D.: Proc. Soc. Exper. Biol. & Med. **36**:787, 1937.

10. Since this paper was submitted for publication (December 1937) it has become clear that impairment of function of the anterior lobe would not materially complicate such experiments because, contrary to one school of thought,[5] a functioning pars anterior is not essential for the occurrence of permanent moderate diabetes insipidus (Keller, A. D.: Proc. Soc. Exper. Biol. & Med. **38**:31, 1938; Am. J. Physiol. **123**:111, 1938. White, H. L., and Heinbecker, P.: ibid. **123**: 213, 1938). This fact was shown particularly well in a series of experiments on 8 dogs, in which we made certain of total hypophysectomy by deliberate infringement on the ventral portion of the hypothalamus. The animals, with a constant food intake, without exception showed permanent polydipsia, drinking from 200 to 300 cc. of water per kilogram of body weight per day. All experiments were continued six months or longer. Complete removal of the pars anterior was evident because (1) sensitivity to insulin was increased twenty times or more, (2) removal of the pancreas resulted in no appreciable diabetes mellitus, (3) basal metabolism was lowered appreciably, and (4) thyroid and adrenal glands showed marked atrophy.

feel on the basis of our own experience with the cat and the dog that the more traumatic the lesion in the hypothalamus the greater is the likelihood that diabetes insipidus will follow. Thus the incidence of severity and permanence of diabetes insipidus following lesions in the ventral hypothalamus, designed to sever all infundibular nerve fibers, is greater for the dog than for the cat. This may well be due to the much greater active vascularization of the hypothalamic region in the dog, which enhances the destructiveness of the lesions.

With reference to the changes encountered in the pars nervosa, the extent of central disappearance of the infundibular process as well as the thinning of the infundibulum was variable and could not be correlated with the extent of the degeneration of the infundibular nerve fibers. This fact is amply demonstrated with reference to the infundibulum in figure 2. Thus, in cat 4 the infundibulum was considerably thinned even though all the nerve fibers were not degenerated. In cats 2 and 3 all the nerve fibers were degenerated; the infundibulum was not encroached on in cat 2 but was markedly narrowed in cat 3. Therefore, the central disappearance of the tissue of the pars nervosa bordering on the infundibular cavity was due to some factor other than the degeneration of the infundibular nerve fibers. We are now certain that this is true of the dog also, because we have succeeded in degenerating all the infundibular nerve fibers, both by a lesion in the ventral hypothalamus and by section of the stalk, without any central disappearance of the tissue of the infundibular process. The increased cellularity, on the other hand, would seem to be in part the direct result of degeneration of the nerve fibers and probably is due to a phenomenon similar to the cellular proliferation which follows any degeneration within the central nervous system.

On the basis of comparative data for the rat and the dog, it is doubtful that the maximum severity of diabetes insipidus for the cat was encountered with cat 5. It seems certain that the polydipsia of this cat was far greater than the maximum encountered by Fisher and Ingram. This may have been merely the reflection of a larger food consumption with a higher salt content than that of the cats in the Chicago series. However, this factor alone hardly seems sufficient to explain this difference in magnitude of the polydipsia encountered.

SUMMARY

The hypophysis was isolated from its entire direct hypothalamic nerve supply in several cats without eliciting any appreciable polydipsia.

10a. Keller, A. D.; Noble, W., and Hamilton, J. W., Jr.: Am. J. Physiol. **117**:467, 1936.

11. Keller, A. D.; Noble, W., and Hamilton, J. W., Jr.: Proc. Soc. Exper. Biol. & Med. **34**:794, 1936.

SERUM THERAPY FOR INFECTIONS WITH STREPTOCOCCI

GENERAL OBSERVATIONS

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In an earlier series of four papers we presented a brief account of our experience up to October 1933 in the treatment of infections due to hemolytic streptococci by use of the concentrated antistreptococcus serum of the New York state department of health. Our results at that time indicated a favorable effect of the serum, although the observations were not regarded as conclusive. We quote a paragraph from the first of these papers:[1]

> In some diseases the natural course of the malady, when uninfluenced by therapeutic meddling, tends to follow a more or less definite schedule and to terminate in recovery or in death. In other disorders the course tends to be variable, and the complications and the eventual outcome are lacking in uniformity. Infections with the hemolytic streptococci belong in the latter category. On that account the appraisal of any therapeutic agent for streptococcic infections is made difficult, and any decisive statement in regard to this matter is calculated to promote controversy rather than conviction.

Certainly more light is needed. The recognition of different serologic types of hemolytic streptococci by Griffith[2] warrants the hope for further improvement in the therapeutic efficiency of serums for infection by these organisms. Evidence indicating the positive value of serum at present available may be expected to encourage further attempts to prepare more potent serum. The use of such serum in conjunction with other therapeutic agents, such as the sulfonamides and

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From the Department of Pathology and Bacteriology, New York Post-Graduate Medical School and Hospital, Columbia University.

1. Sheplar, A. E.; Spence, M. J., and MacNeal, W. J.: Therapeutic Use of Concentrated Anti-Streptococcus Serum of the New York State Department of Health, Arch. Surg. **29**:858-865 (Nov.); 1065-1075 (Dec.) 1934; **30**:1-13 (Jan.); 357-370 (Feb.) 1935.

2. Griffith, F.: Serological Classification of Streptococcus Pyogenes, J. Hyg. **34**:542-584 (Dec.) 1934.

the bacteriophages, challenges investigation. The untoward effects of injections of serum also require further elucidation. Some attention will be given to these questions in the present consideration of our additional cases in which streptococcus serum therapy has been employed since 1933.

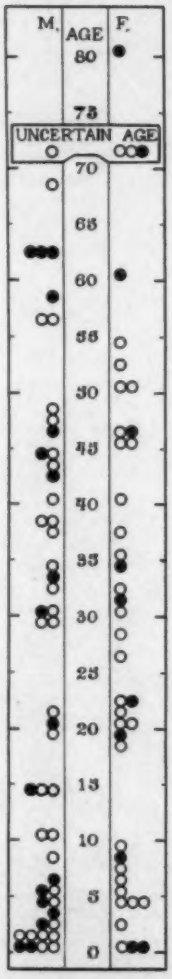

Chart 1.—Distribution according to age and sex of 92 patients treated with streptococcus serum. The hollow circles indicate survivals, and the solid black circles indicate deaths.

The entire series of cases will be presented. It is easy to pick out for exhibition a few startling examples of success and to conceal the failures, thus giving support to the pretense that some particular method of treatment yields miraculous results. We wish not to do this. It is, however, only fair to say that the patients in our series have come

No.	Date	Patient	Sex	Age	Condition at Onset	Operations
	1933					
27	Oct. 16	T. B. H.	M	29	Compound fracture	Oct. 4, Oct. 17
28	Oct. 28	M. P.	F	46	Fracture of right leg; pharyngitis	Nov. 10, Nov. 14, Dec. 8
29	Oct. 31	R. C.	M	14	Mastoiditis	Oct. 31, Nov. 29
30	Nov. 22	S. T.	F	9	Rheumatic fever	None
31	Dec. 7	F. C.	M	Adult	Cellulitis of finger	None
32	Dec. 20	H. H.	F	2½	Cellulitis of right arm	Dec. 20
	1934					
33	Jan. 14	B. F.	M	5	Meningitis	Jan. 13
34	Jan. 17	C. F.	M	15/12	Recurrent otitis media	Previous
35	Jan. 25	A. F.	M	10	Cellulitis of leg	Jan. 23, Mar. 5
36	Jan. 26	P. W.	M	37	Postoperative infection	Jan. 22
37	Feb. 14	K. B.	F	7	Mastoiditis	Feb. 13, Mar. 15
38	Mar. 3	W. R. B.	F	30	Ulcers of leg	None
39	Apr. 7	J. M.	M	10	Meningitis	Apr. 1, Apr. 7
40	Apr. 16	J. D.	M	44	Cellulitis of leg	Apr. 12, 24, May 2
41	Apr. 18	N. M.	F	Child	Meningitis	Apr. 10
42	June 6	L. I.	F	4½	Otitis media	June 5
43	July 1	P. F.	F	8	Peritonitis	June 25
44	July 25	D. M.	F	35	Cellulitis of right leg	July 27
45	July 30	E. O.	F	31	Puerperal sepsis	July 16
46	Aug. 18	L. R.	F	22	Puerperal sepsis	None
47	Nov. 29	E. C.	M	30	Mediastinitis drained	Sept. 30, Oct. 15, Nov. 19, 26, Dec. 4, 10
	1935					
48	Jan. 8	C. F.	M	14	Osteomyelitis, pericarditis	Jan. 6, 23
49	Jan. 11	J. B.	F	80	Mastoiditis, meningitis	Jan. 6
50	Jan. 12	S. S.	F	52	Cellulitis of hand	Dec. 27, 30, Jan. 9, 13,
51	Jan. 12	J. Z.	M	1	Pneumonia; otitis media	Jan. 10, 12, 16, 28, Mar. 28
52	Feb. 15	R. N.	M	62	Mastoiditis; sepsis	Feb. 8, 12
53	Feb. 28	A. C.	F	45	Postoperative	Feb. 24
54	Mar. 2	R. A.	M	1 1/12	Abscess of neck	Feb. 18
55	Mar. 4	M. B.	M	6	Otitis media	Mar. 4
56	Mar. 5	M. L.	M	4	Suppurative knee joint	Mar. 2
57	Apr. 3	W. Y.	M	56	Postoperative	Mar. 11
58	Apr. 10	J. P.	M	11/12	Temperature 106 F. Apr. 9	None
59	Apr. 25	E. R.	M	62	Postoperative	Apr. 18
60	Apr. 29	J. G.	F	4/12	Otitis media; cervical abscess	Mar. 30, Apr. 26
61	May 1	W. F.	M	5/12	Erysipelas	None
62	May 7	E. F.	M	1½	Osteomyelitis	Apr. 22, May 7, 16
63	May 8	R. G.	M	40	Cellulitis of arm	May 10, 13
64	May 11	L. S.	M	5	Otitis media	May 8, 10
65	May 16	C. R.	M	56	Postoperative	Apr. 16
66	May 26	A. P.	F	8/12	Peritonitis	May 25
67	June 5	M. M.	F	4	Otitis media; sepsis	May 31, June 1
68	June 9	M. H.	F	50	Diabetes; abscesses	None
69	July 22	W. L.	M	68	Cellulitis of arm	July 15
70	Sept. 14	L. C.	M	21	Osteomyelitis	Previously
	1936					
71	Jan. 25	J. J.	F	Adult	Pharyngitis	None
72	Jan. 28	A. C.	M	33	Postoperative meningitis	Jan. 23, 26, 28
73	Feb. 10	D. B.	F	22	Pneumonia; empyema; sepsis	Feb. 9, 10, 11, 18, 21
74	Feb. 21	E. M.	F	50	Perforated esophagus	Feb. 13
75	Mar. 18	H. T.	M	14	Empyema	Mar. 13, 30, 31, Apr. 27, 28
76	Mar. 18	T. L.	F	32	Pneumothorax	Feb. 12, 14, 18, 22, Mar. 5, 12
77	Mar. 30	S. R.	M	29	Purulent pararthritis	Mar. 25, 26, Apr. 4, 9, 22
78	Apr. 3	W. H.	M	43	Pharyngitis; otitis media	Apr. 1, 3, 10
79	Apr. 29	W. B.	M	8	Mastoiditis	Apr. 17, 27, May 3, 15
80	Mar. 6	A. S.	F	45	Postoperative; pharyngitis	Apr. 24
81	May 16	J. N.	M	44	Meningitis and mastoiditis	May 15
82	June 15	B. G.	M	20	Fracture of skull; meningitis	June 11, 14, 22
83	Nov. 2	E. S.	M	38	Chronic colitis	None
84	Nov. 25	X. G.	F	34	Leukemia	Jan. 7, 9
	1937					
85	Jan. 14	G. P.	M	32	Sinusitis	Jan. 12
86	Jan. 29	R. W.	F	54	Cellulitis; sepsis	None
87	Feb. 16	V. B.	M	34	Mastoiditis	Feb. 16
88	Feb. 21	E. R.	F	28	Cellulitis of face	None
89	Apr. 18	K. C.	F	40	Cavernous sinus; sepsis	None
90	May 18	B. D.	M	42	Otitis; sepsis; pneumonia; endocarditis (?)	None
91	May 18	P. F.	M	58	Bacterial endocarditis	None
92	July 3	B. S.	F	26	Chronic colitis; rheumatic fever	None

* "N.Y.S. conc." or "N.Y.S. reg." indicates New York state concentrated or regular streptococcus serum; P.D., Parke, Davis & Co. serum, bilological 2005.

Treated with Streptococcus Serum

Positive Blood Culture	Time of Serum Therapy	Serum Used*	Comment
Oct. 12, 16, 19, 25	Oct. 16-Dec. 13	N.Y.S. conc. 118,170 units	Recovered
None	Oct. 28-Dec. 27	N.Y.S. conc. 624,000 units	Died Dec. 27
Oct. 28, 39, Nov. 3, 8, 17	Oct. 31-Nov. 16	N.Y.S. conc. 355,400 units	Recovered
None	Nov. 22-Apr. 24	N.Y.S. conc. app. 24,052 units	Lived
None	Dec. 7-Dec. 10	N.Y.S. conc. 7,500 units	Recovered
Dec. 18	Dec. 20-Dec. 22	N.Y.S. conc. 40,000 units	Recovered
None	Jan. 14-Jan. 21	N.Y.S. conc. 460,000 units	Died Jan. 23
None	Jan. 17-Jan. 26	N.Y.S. conc. 18,900 units	Had prompt relief
None	Jan. 25	N.Y.S. conc. 20,000 units	Recovered
None	Jan. 26-27	N.Y.S. conc. 80,000 units	Recovered
Feb. 12, 13, 14	Feb. 14-Feb. 22	N.Y.S. conc. 240,000 units	Recovered
None	Mar. 3-Mar. 8	N.Y.S. conc. 60,000 units	Unimproved
None	Apr. 7-Apr. 12	N.Y.S. conc. 108,000 units	Recovered
Apr. 16	Apr. 16-Apr. 17	N.Y.S. regular 15,000 units	Recovered
None	Apr. 18-Apr. 23	N.Y.S. conc. 440,000 units	Died Apr. 25
June 4, 6, 7, 8, 18, 20	June 6-June 9	N.Y.S. conc. 200,000 units	Recovered
June 26	July 1	N.Y.S. conc. (1.95 cc.) 3,510 units	"Serum death"
July 30	July 25-July 26	N.Y.S. conc. 51,620 units	Recovered
July 23	July 30	N.Y.S. conc. 3,600 units	Recovered
None	Aug. 18	N.Y.S. conc. 60,000 units	Died. Aug. 19
None	Nov. 29	N.Y.S. conc. 40,000 units	Recovered
Jan. 23, 25	Jan. 26	N.Y.S. conc. 60,000 units	Died Jan. 27
None	Jan. 11-Jan. 13	N.Y.S. conc. 38,000 units	Died Jan. 14
None	Jan. 12	N.Y.S. conc. 65,000 units	Recovered
Jan. 11	Jan. 12-13	N.Y.S. conc. 120,000 units	Recovered
Feb. 11, 15, 16	Feb. 15-16	N.Y.S. conc. 100,000 units	Died Feb. 17
None	Feb. 28	N.Y.S. conc. 40,000 units	Recovered
Mar. 1, 3, 4, 5, 7, 9, 13	Mar. 2-Mar. 8	N.Y.S. conc. and reg. 170,000 units	Recovered
Mar. 4, and others	Mar. 4-14	N.Y.S. conc. 140,000 units	Died Apr. 5
None	Mar. 5-6	N.Y.S. conc. 60,000 units	Recovered
None	Apr. 3	N.Y.S. conc. 25,000 units	Recovered
Apr. 10	Apr. 12-13	N.Y.S. conc. 40,000 units	Recovered
None	Apr. 24-25	N.Y.S. reg. 50,000 units	Died Apr. 25
Apr. 27	Apr. 29-May 3	N.Y.S. conc. 100,000 units	Recovered
May 2	May 1 and May 3-May 7	N.Y.S. reg. and conc. 50,000 units	Died May 8
Staph. pos., Strep. neg.	May 7, 1935-Mar. 19, 1936	N.Y.S. conc. 524,200 units and P.D. 17.5 cc.	Recovered
None	May 8-June 4	N.Y.S. conc. 176,000 units	Recovered
May 9	May 11-July 11	N.Y.S. conc. 804,400 units	Recovered
None	May 16, 20, 29, June 2	N.Y.S. reg. 70,000 units	Recovered
May 25	May 26	N.Y.S. conc. 40,000 units	Died May 26
June 2, 16	June 5-June 17	N.Y.S. conc. 150,000 units	Recovered
None	June 9-June 12	N.Y.S. conc. 20,000 units	Recovered
None	July 22-July 31	Eli Lilly	Recovered
None	Sept. 14, 1935, Jan. 24, 1937 and Mar. 6, 1937	P.D. 23.63 cc.	Improved
None	Jan. 25-Jan. 26	P.D. 20 cc.	Recovered promptly
None	Jan. 28-Jan. 30	P.D. 49 cc.	Died Jan. 31
Feb. 10	Feb. 10-Apr. 6	P.D. 760 cc.	Healed
None	Feb. 21-Mar. 3	P.D. 85.6 cc.	Improved
None	Mar. 18-May 31	P.D. 157.85 cc.	Recovered
None	Mar. 18-Mar. 27	P.D. 87 cc.	Recovered
None	Mar. 30-June 30	P.D. 8.242 cc.	Improved
None	Apr. 3-May 19	P.D. 150.71 cc.	Recovered
Apr. 29	Apr. 30-May 18	P.D. 2 cc., N.Y. reg. 91,500 units	Recovered
None	May 6-May 20	P.D. 14.54 cc.	Recovered
None	May 16	P.O. 26 cc.	Died May 17
None	June 15-June 19	P.D. 41.005 cc.	Died June 26
None	Nov. 4-Jan. 23	P.D. 102.2 cc.	Improved
None	Nov. 25-Feb. 2	P.D. 322.9 cc.	Died Feb. 3
None	Jan. 14-Jan. 21	P.D. 13.1 cc.	Recovered
Jan. 28	Jan. 29-Feb. 9	P.D. 18.55 cc.	Cellulitis cured
None	Feb. 16-Feb. 28	P.D. 15.6 cc.	Had rapid healing
None	Feb. 21-Feb. 28	P.D. 26.81 cc.	Recovered
Apr. 16	Apr. 18-May 29	P.D. 238.5 cc.	Recovered
May 7, 8, 22, June 6	May 18-June 13	P.D. 340 cc. N.Y.S. conc, 136,980 units	Died June 14
Repeated Str. viridans	May 18-July 4	P.D. 48.7 cc.	Died July 7
None	July 3-Aug. 7	P.D. 7.33 cc.	Improved

to our attention not in the course of private clinical service but by reference or by request for consultation and, in general, only after the condition had been recognized as desperate. In our earlier report we presented the records of 26 patients. For the present discussion there are data on 66 further patients. The cases are listed in chronologic order, according to the date of institution of serum therapy, in the accompanying table. Various clinical conditions are represented. We purpose to group the cases according to regional specialty and to discuss in more detail each such group in the subsequent papers of this series. In the present paper only the more general features will be discussed.

The age and sex distribution of the entire 92 patients, including the 26 of our previous report and the present 66, is indicated in chart 1. The youngest patient was a boy aged 19 days and the oldest a woman aged 80 years. Evidently there is no exemption from streptococcic infection at any age or in either sex.

In the present group of 66 patients, 18 died and 48 recovered from the streptococcic infection; the death rate, therefore, was 27.3 per cent. Some of the deaths were evidently due to causes not directly related to infection with hemolytic streptococci, while others were due to such infection which was not controlled by treatment. A brief review of each fatality will be undertaken.

REPORT OF CASES

CASE 62.—W. F., a boy aged 5 months, was admitted to the hospital on April 30, 1935, with an infection of the upper respiratory tract, present since April 23. On admission there was purulent rhinitis. There were also swelling of the right lower part of the face and erysipelas of the face, the neck and the upper part of the thorax. On May 1, 10.5 cc. of erysipelas antitoxin (Squibb) was given in divided doses into muscle. On May 2, a culture of the blood was made, which later gave a positive growth of hemolytic streptococci. Another ampule of erysipelas antitoxin was given on this day. On May 3, as the culture of the blood was yielding bacteria, a transfusion of 150 cc. was given and also 10,000 units of the concentrated streptococcus serum of the New York state department of health. The child was exposed to ultraviolet radiation for two minutes. The dose of serum was repeated on May 4. On May 5 a culture of the blood was taken, and this remained sterile; 20,000 units of the same serum was given. On May 6, the culture remaining sterile, the concentrated serum was discontinued, and 5,000 units of unconcentrated streptococcus serum (New York state) was given intravenously. This dose of serum was repeated on May 7, intravenously. The baby died at 2:45 p. m., May 8. Permission for necropsy was not obtained. The clinical diagnosis at the end was pneumonia of the upper lobe of the left lung.

CASE 67.—A. P., a girl aged 8 months, was admitted to the hospital on May 25, 1935, with high fever (temperature 104.6) and a distended, tense abdomen. Laparotomy on this same day disclosed generalized peritonitis without recognizable primary focus. Cultures of the blood and of the peritoneal fluid gave a positive growth of hemolytic streptococci. On May 26, when these cultures had developed, we were asked to see the infant. Concentrated streptococcus serum (New York state), 40,000 units, was given in divided doses, and 30 cc. of stock streptococcus

bacteriophage in asparagine medium was introduced into the peritoneal cavity along the surgical drain. The patient died at 11:45 p. m., May 26. Necropsy was not permitted.

CASE 33.—B. F., a boy aged 5 years, was admitted to the hospital on Jan. 12, 1934, with otitis media on the left side, a temperature of 104.6, and signs of meningitis. A spinal tap on this day yielded cloudy spinal fluid containing hemolytic streptococci. On January 13 a mastoidectomy was done on the left side. On January 14, treatment with concentrated streptococcus serum (New York state) was started, 20,000 units into the spinal canal and 20,000 units intravenously, and the serum was continued daily through January 21, in increased amount toward the last, to a total of 200,000 units into the spinal canal and 260,000 units intravenously. The patient died January 23 at 3:30 a. m., and necropsy disclosed generalized purulent meningitis and bronchopneumonia of the lower lobe of the right lung.

CASE 56.—M. B., a boy aged 6 years, was admitted to a hospital in Westchester County on Feb. 27, 1935, with otitis media and a temperature of 104 F. Mastoidectomy was performed on March 4. Cultures of the blood made on March 4 and several times thereafter gave a positive growth of hemolytic streptococci. Concentrated streptococcus serum (New York state) was given in the period from March 4 to March 14, a total amount of 140,000 units. Apparently it was then discontinued. Bronchopneumonia and multiple pulmonary abscesses developed. The child died April 5.

CASE 43.—P. F., a girl aged 8, was admitted to the hospital on June 25, 1934. On the next day laparotomy was performed and the appendix was removed. Generalized peritonitis without recognizable focus was present. Hemolytic streptococci were found in culture of the peritoneal fluid and also in culture of the blood. Concentrated streptococcus serum (New York state) was given on July 1, producing fatal anaphylactic shock. (This case will receive more detailed consideration when we come to discuss serious untoward serum reactions and their prevention.)

CASE 41.—N. M., a girl aged about 10 years, was seen by us at Dobbs Ferry, N. Y., on April 18, 1934. Spinal tap at this time yielded a turbid fluid containing hemolytic streptococci. Concentrated streptococcus serum (New York state) was administered into the spinal canal and intravenously. The patient seemed to improve for a time, but we learned subsequently that she died April 25, 1934.

CASE 49.—C. F., a boy aged 14, was admitted to a hospital on Jan. 4, 1935, with osteomyelitis of the right ilium. He had been ill since Dec. 30, 1934. Cultures of blood on January 4 and January 5 gave a positive growth of staphylococci. On January 5 an operation for drainage of the ilium and counterdrainage of the hip was performed, and a transfusion was given. The temperature reached 106. Staphylococcus bacteriophage was administered. On January 23 pericardostomy was performed. A culture of the blood was reported on January 26 as yielding streptococci but not staphylococci. Concentrated streptococcus serum (New York state), 60,000 units, was given on January 26. The patient died January 27.

CASE 82.—B. G., a man aged 20, was injured in an automobile accident May 30, 1936, and was transferred to the New York Post-Graduate Medical School and Hospital on June 10, 1936. On June 11 a bilateral cerebral exploration was performed without discovery of any purulent focus. On June 13 pus was aspirated from an abscess over the sacrum; this pus contained hemolytic streptococci. Bacteriotherapy was requested and initiated on June 15, and streptococcus serum (Parke, Davis & Co., biological 2005) was given daily from June 15 to June 19, the total amount being 41.005 cc. The sacral lesion improved. A sup-

purating laceration of the face contained staphylococci, and on this account staphylococcus bacteriophage was administered on June 23 and 24. The patient died on June 26, and at necropsy, in addition to the external lesions of the face and the sacrum and the surgical wounds of the skull, there was disclosed a fracture of the base of the skull with basilar meningitis apparently extending from a lacerated sphenoid sinus.

Case 47.—L. R., a woman aged 22, was a private patient whom we did not see. She was delivered of a child at 8:11 p. m. on Aug. 5, 1934. Her temperature remained normal until 8 a. m. on August 8 and then rose, reaching 104.4 F. at 8 p. m. on that day. Cultures of material from the uterine cervix on August 14 yielded a growth of Streptococcus viridans and Staphylococcus albus. Another culture made from the uterine discharge on August 17 yielded a growth of hemolytic streptococci. No culture of the blood yielding bacteria was ever obtained. Pneumonia was recognized on August 16, and it became progressively more serious. On August 18 concentrated streptococcus serum (New York state) was given in divided doses to a total amount of 60,000 units, without evident effect. The patient died at 12:15 p. m. on August 19.

Case 72.—A. C., a man aged 33, was admitted to the hospital on Jan. 22, 1936, and on January 23 a laminectomy was performed for neoplasm of the spinal cord. On January 26 the surgical wound was found to be grossly infected, and revision of the wound disclosed an abscess containing 10 to 15 cc. of pus. The cultures yielded hemolytic streptococci. A culture of blood made on January 27 remained sterile. On January 28 further revision of the wound released more purulent collections. Streptococcus serum (Parke, Davis & Co., biological 2005) was given intravenously after the usual series of desensitizing doses, a total amount of 19 cc. on January 28, 10 cc. on January 29 and 10 cc. on January 30. The patient died January 31. Necropsy was not permitted.

Case 84.—X. G., a woman, aged 34, the wife of a physician, was admitted to a neighboring hospital on Nov. 25, 1936. She had a persistent extensive and deep ulceration of the left side of the mouth and the blood picture of myelogenous leukemia with high grade anemia. The gangrenous ulcer of the mouth contained a mixture of micro-organisms, among which hemolytic streptococci, staphylococci, fusiform bacilli and spirochetes were conspicuous. Along with daily transfusions and chemotherapy with sulfanilamide and neoarsphenamine the patient received staphylococcus bacteriophage and streptococcus serum (Parke, Davis & Co., biological 2005). The total amount of serum used was 323 cc. It was given daily from Nov. 25 to Feb. 2, 1937. The patient died February 3, early in the morning, apparently from meningitis caused by extension of the lesion of the mouth into the left orbit and along the optic nerve. An attempt at surgical drainage of the orbit had been made. Bacteriologic examinations of the slowly progressive lesion indicated the suppression of the streptococci and the staphylococci. For a time there seemed to be relative remission of the leukemia, but the blood picture of leukemia again returned shortly before death.

Case 90.—B. D., a man aged 42, was admitted to the New York Post-Graduate Medical School and Hospital on May 17, 1937, by transfer from another hospital. Early in April he had pharyngitis, and later, otitis media on the right side and spontaneous rupture of the tympanic membrane. Early in May he had a severe chill, and he entered the first hospital on or about May 6. Repeated cultures of the blood yielded hemolytic streptococci. On May 11 a roentgenologic diagnosis of bilateral mastoiditis was made. The temperature ranged from 99 to 106. Sulfanilamide, 15 grains every three hours by mouth, and prontosil soluble (the disodium salt of 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonic acid) 50 cc. every twenty-four hours in divided intramuscular doses

was administered. The patient became cyanotic. On May 13 pneumonia and pleurisy in the right lower quadrant of the thorax were so distressing that this side was taped. The patient was transferred to the New York Post-Graduate Medical School and Hospital May 17, in an unsatisfactory condition, in the hope that serum therapy might be of help. On May 18 a culture of the blood was made, and this remained negative. Methemoglobin was detected by spectroscopic examination of the blood. Cultures of the blood made on May 22 and June 6 yielded bacteria. The painful pleurisy on the right side disappeared, but the physical signs of airless portions of lung persisted. Roentgen study of the thorax revealed patches of infiltration in both lungs but no evidence of pleural effusion. A thoracentesis on the right side was done on June 7, but only 3 cc. of bloody fluid, containing a few flakes of fibrinopurulent membrane, could be obtained. Irregular cardiac action, rapid pulse, low and variable blood pressure and paroxysmal dyspnea, together with the patchy distribution of the pneumonia, led to the strong suspicion of tricuspid vegetative endocarditis. The patient died at 7:20 a. m., June 13. Necropsy was not permitted, so the scientific value of the case is seriously impaired.

Because of the apparently unfavorable progress and the evident methemoglobinemia, the administration of sulfanilamide was interrupted on May 17. Streptococcus serum (Parke, Davis & Co., biological 2005) was given in divided doses on May 18 to a total amount of 25.15 cc. and was continued daily until June 2, the total amount used being 340 cc. for the sixteen days. Subsequently the concentrated serum of the New York state department of health was used, from June 3 to June 13 inclusive, the total amount being 76.1 cc. in eleven days. Sulfanilamide was again given by mouth on May 23 and thereafter; prontosil soluble was injected intravenously, and a specific bacteriophage prepared for the streptococcus yielded by culture of the patient's blood was used intravenously, beginning on June 3. Transfusions were given daily from June 3 to June 13. Various consultants saw this patient during his illness. There were no important differences of opinion.

Case 81.—J. N., a man aged 44, was admitted to the hospital April 28, 1936, with chronic inflammation of the paranasal sinuses, acute pharyngitis and an abscess along the lower jaw. On May 6 the abscess was incised. On May 15 the patient had a chill lasting thirty minutes and became stuporous. A culture of the blood, made at this time, remained sterile. Spinal tap yielded cloudy fluid showing pus cells and streptococci in the direct microscopic examination and, on culture, hemolytic streptococci. At 12 midnight a simple mastoidectomy was performed, and cultures of material from the mastoid also showed streptococci. On May 16 serum therapy was requested, and multiple doses to a total amount of 26 cc. were given from 12:38 to 3:48 p. m. The patient then went into a chill lasting thirty minutes, and the serum was discontinued for the day. He died at 4 a. m. on May 17. Necropsy was not permitted.

Case 28.—M. P., a woman aged 46, was admitted to the hospital on Oct. 27, 1933, with compound fracture of the right leg, acute pharyngitis and a temperature of 104.8 F. Concentrated streptococcus serum (New York state) was given in divided doses on October 28 to a total of 37,000 units and was continued from October 30 to November 5, at which time the infection seemed to be controlled. After a transfusion on November 8, an operative revision of a slough was undertaken on November 10 and another on November 14. Evidence of renewed local inflammation led to the request for further serum therapy, and this was begun on November 15 and continued almost daily to the end. Soluble phenobarbital U. S. P. (sodium phenobarbital) was given on November 1 and November 3; sodium amytal was given, beginning on November 10, for distressing pain

in the leg, and the doses of barbiturates were considerably increased after a further surgical revision of the wound in the leg on December 8. The danger of barbiturate therapy was not appreciated at that time (November 1933).

The blood count on November 6 showed 2,800,000 erythrocytes and 48 per cent hemoglobin; 12,550 leukocytes and 82 per cent of polymorphonuclears. On November 9, after transfusion on the previous day, the erythrocytes numbered 3,150,000 and the hemoglobin was 62 per cent; the leukocytes numbered 7,850, with 72 per cent polymorphonuclears. On November 22, twelve days after the administration of sodium amytal was started, the leukocyte count was 4,100, with 11 per cent polymorphonuclears. Pentnucleotide was given. On November 27 the leukocyte count was 4,800, with 36 per cent polymorphonuclears, and on November 29 it was 7,700, with 38 per cent polymorphonuclears. After the operation on

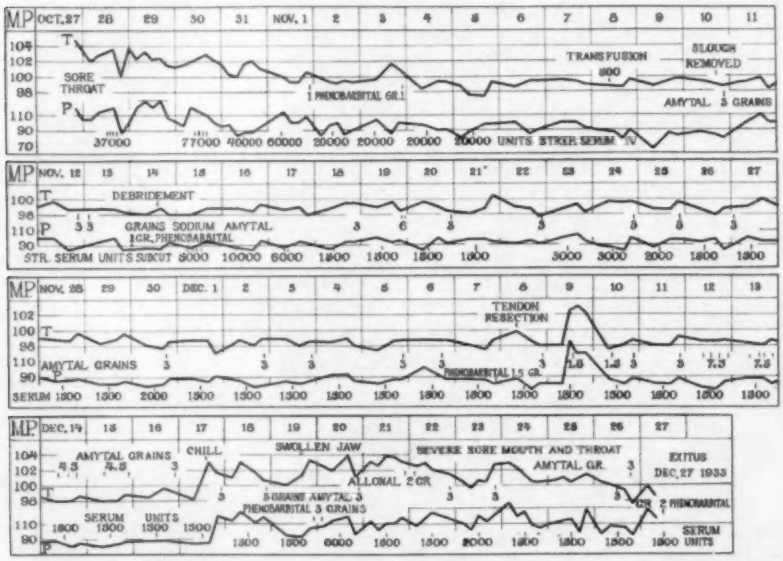
M.P
OCT. 27 28 29 30 31 NOV. 1 2 3 4 5 6 7 8 9 10 11
SORE THROAT
1 PHENOBARBITAL GR. 1
TRANSFUSION 800
SLOUGH REMOVED
AMYTAL 3 GRAINS
37000 77000 40000 60000 20000 20000 20000 20000 UNITS STREP. SERUM IV
NOV. 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27
DEBRIDEMENT
GRAINS SODIUM AMYTAL 1 GR. PHENOBARBITAL
STR. SERUM UNITS SUBCUT 8000 10000 6000 1800 1800 1800 1800 3000 3000 2000 1800 1800
NOV. 28 29 30 DEC. 1 2 3 4 5 6 7 8 9 10 11 12 13
TENDON RESECTION
AMYTAL GRAINS
PHENOBARBITAL 1.5 GR.
SERUM 1800 1800 2000 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800
DEC. 14 15 16 17 18 19 20 21 22 23 24 25 26 27
AMYTAL GRAINS
CHILL
SWOLLEN JAW
SEVERE SORE MOUTH AND THROAT
AMYTAL GR. 3
EXITUS DEC. 27 1933
ALLONAL 2 GR.
5 GRAINS AMYTAL 3 PHENOBARBITAL 3 GRAINS
2 PHENOBARBITAL
SERUM UNITS
SERUM UNITS

Chart 2 (case 28).—Abridged clinical record of M. P., a woman aged 46. The infection present on admission seemed to respond well to serum therapy, and the recrudescences of the infection following surgical treatment of the leg on November 10, November 14 and December 8 seemed to be controlled in a satisfactory manner. Agranulocytosis became evident on November 22, and this was evidently the chief factor in bringing about the fatal termination.

December 8 the dose of sodium amytal was increased somewhat. Examinations of the blood disclosed a progressive fall of the percentage of polymorphonuclear leukocytes, as follows:

Date	Leukocytes	Polymorphonuclears, %
Dec. 11	4,050	54
Dec. 13	8,850	42
Dec. 14	8,250	17
Dec. 15	7,500	16
Dec. 16	6,400	2
Dec. 18	3,250	0

After this date polymorphonuclear leukocytes were not again seen in the blood of this patient. On December 20 the gums became swollen and painful. Progressive ulceration soon appeared in the mouth and pharynx, and the tissues about the lower jaw and the neck became swollen. On December 21 perianal edema was noted. The patient died December 27. At necropsy there was extensive ulceration in the mouth, the pharynx, the small intestine and the large intestine, with hemorrhage into the intestine. The total amount of streptococcus serum used in this case was 624,000 units. It is evident that the serum did not furnish protection from the dangers of toxic agranulocytosis.

Case 91.—P. F., a man aged 58, was admitted to the hospital on May 17, 1937, with aortic vegetative endocarditis, Str. viridans in the blood stream, aphasia and residual hemiplegia from a cerebral insult which had occurred about April 10, 1937. In conjunction with other therapeutic measures, small doses of streptococcus serum (Parke, Davis & Co., biological 2005) were given daily without any evident effect. After a second stroke, on June 23, the patient died on July 7. Necropsy disclosed active vegetations on the aortic valve, bilateral softening of the internal capsule of the cerebrum, due to embolic block of both middle cerebral arteries, old on the left side and more recent on the right side.

Case 53.—R. N., a man aged 62, was admitted to the hospital on Feb. 8, 1935, because there had been a discharge from his left ear since Dec. 8, 1934. Mastoidectomy was performed on the day of admission, and culture of material from the mastoid gave a growth of hemolytic streptococci. On February 10 the patient had a chill. A culture of the blood made on February 11 gave a positive growth of hemolytic streptococci, about twelve colonies per cubic centimeter of blood. On February 12 the left jugular vein was resected, the mastoidectomy wound was reopened and a transfusion of 500 cc. was given. On February 14 there was clinical evidence of pneumonia and of periarticular inflammation at the left knee. On February 15 another culture of the blood was made, which yielded bacteria. On this day a transfusion of 250 cc. was given and concentrated streptococcus serum (New York state) was administered, 20,000 units subcutaneously and 20,000 units intravenously. On February 16 a culture of the blood was made and yielded 400 colonies per cubic centimeter of blood. Concentrated streptococcus serum (New York state), 20,000 units, was given intravenously. The patient died at 9 a. m., February 17.

Case 60.—Z. R., a man aged 62, was admitted to the hospital April 23, 1935, with redness and swelling of the skin over the back, extending from the shoulders to the waistline, and a sloughing ulcer over the left scapula at the site of a surgical wound where a papillary nevus had been removed on April 18, 1935. On April 24 exudate from the wound showed streptococci on microscopic examination, and the culture subsequently produced colonies of hemolytic streptococci. The urine contained 5.2 per cent sugar on April 24. A culture of the blood made on the same day remained sterile. A transfusion of 330 cc. and regular (unconcentrated) streptococcus serum (New York state), 25,000 units, were given on April 24, and the same dose of serum was given again on April 25. The patient died at 3:25 p. m., with signs of gradually increasing pulmonary edema. Necropsy was not permitted.

Case 50.—J. B., a woman aged 80, was admitted to the hospital on Jan. 4, 1935. Mastoidectomy was performed on January 6. After the operation the temperature rose, reaching 106 F. on January 9. On this day a spinal tap yielded cloudy fluid containing 2,500 white cells per cubic millimeter and also microscopically visible streptococci. Serum therapy was requested on January 11, and

regular unconcentrated streptococcus serum (New York state) was given on January 11, 12 and 13 to a total amount of 38,000 units. Death occurred at 2: 40 a. m. January 14. Necropsy was not permitted.

These brief notes on the cases in which death occurred are sufficient to indicate the desperate situation at the beginning of serum therapy in many of them. Such treatment represented little more than a gesture or perhaps a forlorn hope for the patients with meningitis (cases 33, 41, 82, 72, 81 and 50) and those with generalized peritonitis (cases 67, 43, 2 and 5). Certainly little or nothing was to be expected in the treatment of the patient in case 49, with terminal streptococcic sepsis after pericardostomy for staphylococcic sepsis; in that of the patient in case 84, suffering from leukemia and gangrenous stomatitis, or in that of the patient in case 91 with vegetative endocarditis and hemiplegia. In cases 62 and 56 the dose of serum was reduced or discontinued after culture of the blood became sterile, and the patients died of pneumonia, probably of septic origin. In case 28 the streptococcic infection was controlled, but the patient succumbed, death being due apparently to toxic agranulocytosis. In case 47, in which the patient had puerperal fever and pneumonia, the specific diagnosis of streptococcic infection was uncertain, and the serum was administered as a forlorn hope on the eve of her death. In 3 instances, although serum therapy was initiated rather late, one has to acknowledge frank failure (cases 90, 53 and 60). There was no attempt to select favorable cases and no thought of refusal to undertake serum therapy because of the desperate or even apparently hopeless nature of the condition.

The 56 patients who survived had various clinical conditions. In subsequent papers we plan to discuss these in special groups according to the region of the body primarily involved. However, it seems best to discuss a few of the successful cases at this place in order to illustrate the technical procedure and to indicate what may be expected from the use of a serum under more fortunate circumstances.

Case 32.—H. H., a girl aged 2½ years, was admitted to the hospital on Dec. 18, 1933. On December 4 she had an infection of the left index finger, and since December 11 there had been a swollen gland in the left side of the neck and some fever every day. On December 18 the right elbow became swollen. On admission there were old infected lesions on both index fingers and a tender swelling about the right elbow, with limitation of motion. There was a red area on the lateral aspect, which appeared to be the pointing of an abscess. The tonsils were enlarged and inflamed. The temperature on admission was 104.8 F. A culture of the blood made December 18 gave a growth of streptococci with narrow zones of hemolysis. The urine contained a trace of protein and 20 to 30 leukocytes per high power microscopic field. Roentgenologic examination did not reveal any changes in bone. On December 20 a paracentesis of the right elbow failed to obtain any pus. Concentrated streptococcus serum (New York state), 20,000 units, was given subcutaneously, without reaction. A culture of the blood made on this day remained sterile. On December 21 a transfusion of 225 cc. was given. On December 22

another subcutaneous injection of the same serum, 20,000 units, was given. A culture of the blood made on this day remained sterile. By December 26 the swelling of the elbow and of the cervical gland had subsided. On December 30 an erythematous rash appeared on the left arm and the left thigh, and this was generalized on December 31 and January 1. Fever was present on January 1. This was evidently the manifestation of serum disease. The rash promptly subsided, and the temperature remained normal after January 2.

Case 73.—D. B., a woman aged 22, was admitted to the hospital on Feb. 7, 1936. She had an infection of the upper respiratory tract about January 31 and classic pneumonia on February 4. On admission she was semicomatose. The respiratory rate was 26, the pulse rate 100 and the temperature 100.4 F. The left side of the chest was dull to percussion everywhere posteriorly. The heart sounds were pure; the rhythm was regular, and the blood pressure was 95 systolic and 60 diastolic. The leukocyte count was 24,350, with 95 per cent polymorphonuclears. Examination of the sputum revealed hemolytic streptococci in almost pure culture. On February 9 at 2 p. m. a thoracentesis (on the left) yielded 450 cc. of cloudy yellow fluid, thoracentesis was repeated at 10 p. m., when 650 cc. of fluid was removed. Culture of these fluids yielded hemolytic streptococci. On February 10 a culture of the blood was made, and this also gave a positive growth of hemolytic

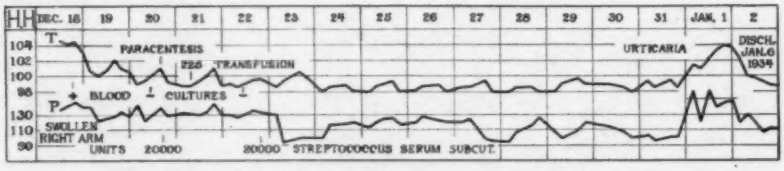

Chart 3 (case 32).—Abridged clinical record of H. H., a girl aged 2½ years. This child was admitted with bacteremia apparently originating from infection of the fingers. The progress of the case was satisfactory, but it is uncertain whether the patient might not have done well without the serum. The fever and rash on December 31 were evidently manifestations of serum disease. They subsided promptly.

streptococci. The white cell count was now 42,800. At this point serum therapy was requested, and the serum[3] was administered as follows on February 10:

5:21 p. m.	0.1 cc. of 1:10 dilution intracutaneously; reaction negative
5:32 p. m.	2.0 cc. of 1:10 dilution subcutaneously
5:45 p. m.	3.0 cc. of 1:10 dilution into muscle
5:58 p. m.	5.0 cc. of 1:10 dilution into muscle
6:12 p. m.	1.5 cc. undiluted into muscle
6:27 p. m.	3.5 cc. undiluted into muscle
6:38 p. m.	1.0 cc. of 1:10 dilution intravenously
6:47 p. m.	3.0 cc. of 1:10 dilution intravenously
7:01 p. m.	6.0 cc of 1:10 dilution intravenously
7:16 p. m.	3.0 cc. of 50 per cent dilution intravenously
7:29 p. m.	7.0 cc. of 50 per cent dilution intravenously
7:46 p. m.	7.0 cc. of undiluted serum intravenously
8:00 p. m.	10.0 cc. of undiluted serum intravenously

3. The concentrated streptococcus serum of Parke, Davis & Co. (biological 2005) was used throughout for this patient.

Thus in thirteen doses at approximate intervals of fifteen minutes a total equivalent to about 30 cc. of the undiluted serum was given during two hours and thirty-nine minutes. Fifteen minutes after the last injection the patient had a chill which lasted forty minutes. Oxygen and epinephrine were administered. The temperature rose during the chill to 106.8 F. The patient then began to perspire freely, and the temperature fell to 101 F. in four hours.

This type of reaction we consider favorable. It seems to be identical with the reaction observed frequently when an infection of the blood stream is successfully treated by progressive series of intravenous injections of potent bacteriophage. It also seems to be the same as the reaction observed by Young [4] and his collaborators when they injected intravenously the amount of mercurochrome suitable to initiate recovery in septic patients. One is therefore inclined to think that this visible

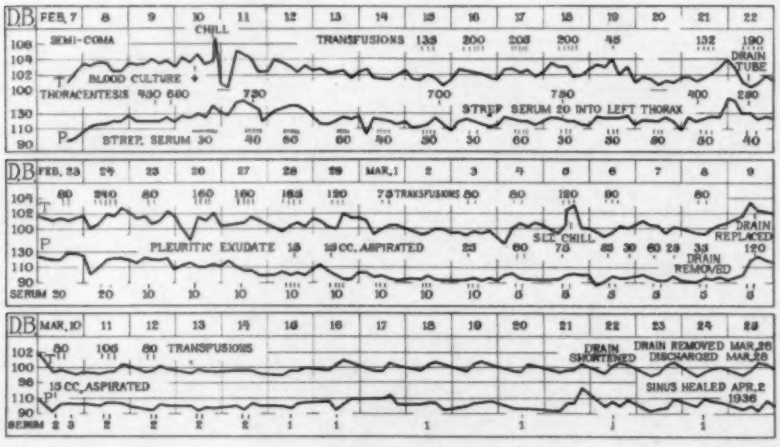

Chart 4 (case 73)—Abridged clinical record of D. B., a woman aged 22. There were pneumonia of the left lung and empyema on admission, and the prognosis was grave on February 10, at which time serum therapy was requested. The series of intravenous injections of serum on this day was followed by a shock reaction (Hugh Young reaction) which marked the turning point in the disease. Desperate measures, however, were still required for its control. After several taps, a drainage tube was inserted into the pleural cavity on February 22. Continuation of the intravenous serum and the fractional transfusions are indicated on the chart. The final result was most gratifying.

reaction is the external manifestation which indicates a turning of the balance in the fight between the bacteria on the one hand and the protective body fluids and phagocytic cells on the other hand, probably due to an injury inflicted on the invading bacteria by the therapeutic agent,

4. Young, H. H.: The Treatment of Infections—General, Local and Urinary—with the Intravenous Injection of Mercurochrome, Surg., Gynec. & Obst. **40**: 97-104 (Jan.) 1925.

be it serum, phage or chemical poison. As one gets more experience in the intravenous administration of such therapeutic agents one learns to expect this reaction as the culmination of the series of progressively increasing intravenous injections. The prolonged vigorous chill with its distressing cyanosis and air hunger, the high elevation of the temperature and the sudden reddening warmth of the skin at the end, followed by drenching sweat and a spontaneous fall in temperature, constitute a reactive phenomenon so often repeated in successive cases as eventually to be recognized as a distinct reaction to effective intravenous therapy for bacteremia. Undoubtedly this reaction has much in common with the ordinary spontaneous chill, temperature spike and sweat so often repeated in untreated septic disease and in the earlier weeks of malaria, and one may sometimes be unable to distinguish between such reactions when giving intravenous treatment. The timing is, however, significant, and if the therapeutic injections are given in regularly and gradually increasing doses at regular intervals until the chill appears, the true nature of the phenomenon will usually become manifest. Without pretending that this is in any just sense a new phenomenon, we nevertheless believe that the association of this reaction with intravenous therapy directed against the infecting microbe in bacteremia is something which belongs essentially to the more modern era in therapeutics, and we therefore suggest that this rather typical series of manifestations marking the successful termination of a series of intravenous injections be designated as the Hugh Young reaction. A further proof of the character of this phenomenon is of course furnished by the subsequent steady improvement in the clinical condition of the patient and the eventual complete recovery, which is, however, not to be expected without further intelligent and adequate care.

For the patient at present under consideration the ominous return to a temperature of 105 F. at 8 a. m. on February 11 served as a warning against premature relaxation of therapeutic efforts. On this day eight intravenous injections of equal amounts of serum were given at intervals of approximately one hour, to a total amount of 40 cc. For convenience of injection through a needle of gage 27 the serum was diluted with an equal volume of sterile saline solution. Late in the afternoon the chest was again tapped, and 750 cc. of fluid was removed. The patient was more alert and cooperative. As shown in the chart, the large doses of serum were continued every day. The patient did so well that there was some hope of avoiding surgical drainage of the thorax. Beginning on February 15, fractional transfusions were given almost every day until March 12. The left pleural cavity was tapped again on February 18, and 750 cc. of thin, purulent fluid was obtained. It was decided to insert a rubber tube for continuous drainage of the pleural cavity. On February 21, accordingly, a trocar was introduced, and a rubber drain was inserted through the cannula. About 400 cc. of a moderately thick, greenish purulent fluid was obtained at this time, and abundant purulent drainage continued to come away through the rubber tube. Irrigation of the pleural cavity with a proprietary solution of sodium hypochlorite and saline solution was practiced daily beginning on February 27. A roentgenogram taken on

February 27 showed partial collapse of the left lung with consolidation of the lower lobe, moderate pleural exudate at the base and a well established pneumothorax. The drainage tube was shortened from time to time and was removed on March 8. However, because of evident accumulation of fluid and a rise in temperature and in pulse rate the tube was again inserted on the following day, when 120 cc. of purulent fluid was obtained. After progressive shortening of the tube it was finally dispensed with on March 26, and the patient was discharged March 28. She returned to receive an injection of serum on April 2, at which time the thoracic opening was found to be closed and entirely covered by epidermis, so that no further dressing was required.

This patient was able to take large amounts of the serum in divided doses. She became moderately sensitive to the serum, and a moderate rash appeared on February 20, but the diminution in amount of serum after February 22 was made not because of her sensitivity but rather because of economic considerations. The outcome was unexpectedly satisfactory. There is only a small scar, and the patient has remained in excellent condition since leaving the hospital. The total amount of concentrated streptococcus serum used was 760 cc., and the total amount of human blood used in transfusions was 2,902 cc.

Case 66.—C. R., a man aged 56, was admitted to the hospital on March 28, 1935, with carcinoma of the glans penis. He had worked at shoveling coal for twenty years. On April 17 amputation through the middle of the shaft and bilateral dissection of the inguinal nodes were performed. Examination of the specimens revealed squamous cell carcinoma of the glans and metastatic extension to the right inguinal nodes. There was considerable postoperative edema, but the patient was out of bed by April 29 and was apparently in good condition. On May 3 the temperature suddenly rose to 104 F. The wounds appeared clean, but there was considerable edema of the scrotum and stump of the penis. On May 4 exudate from both inguinal wounds was taken for bacteriologic study. That from the left side was sterile, but that from the right side yielded a growth of hemolytic streptococci. Culture of material taken from the left inguinal wound on May 8 also gave a growth of the same organism. On May 9 the temperature rose again and remained elevated. Brawny, dark red induration extended to the thighs on May 15. Regular (unconcentrated) streptococcus serum (New York state) was given in divided doses on May 16, intracutaneously at 3:10 p. m., subcutaneously at 3:30 p. m., intramuscularly at 3:45 p. m. and intravenously at 3:55 p. m., 4:05 p. m. and 4:30 p. m., to a total amount of 25,000 units. No reaction occurred. The patient was evidently improved by the next day, and the serum was discontinued. On May 20, another ampule of the same unconcentrated serum (5,000 units) was given intravenously without evident reaction. The patient did well until May 26, when again the temperature rose, and there was an extension of the cellulitis to the lower part of the right leg, which became swollen, red and hot on the morning of May 29. The same serum was again administered, this time in divided doses to guard against anaphylactic shock, to a total amount of 15,000 units. Improvement followed at once, but this time the injections of serum were continued daily until June 2. The patient was discharged on June 3 in good condition.

Case 36.—P. W., a man aged 37, was admitted to the hospital on Jan. 21, 1934, and a bilateral Bassini herniotomy was performed on January 22. The temperature rose to 104.4 F. on January 23. Cultures of material from the operative wounds were made on January 24 and showed abundant hemolytic streptococci, which were found partially susceptible to streptococcus bacteriophage. On January 26 the bacteriophage was applied to the wounds through the drainage tubes

at 3:15 p. m. and again at 6 p. m. and 7 p. m. At 7 p. m. concentrated anti-streptococcus serum (New York state) was given intramuscularly (40,000 units). At 8 p. m. a culture of the blood was made, which remained sterile. After midnight, the bacteriophage was given through the drainage tubes, at 12:45 a. m., 3 a. m., 6 a. m., 9 a. m. and 12 noon on January 27. The concentrated serum, 40,000 units, was given intramuscularly at 1 p. m. No further serum was used, but the local application of the bacteriophage preparation was continued several times each day until February 3, when this also was discontinued. The further course was uneventful, and the patient was discharged February 12 in good condition.

Case 86.—R. W., a woman aged 54, was admitted to the hospital on Jan. 28, 1937, with signs of extensive cellulitis of the right arm and forearm. A culture of the blood, made at about 3 p. m. on January 28, showed the next day a positive growth of hemolytic streptococci. At 12 noon on January 29 another culture was made, and this one remained sterile. Immediately afterward, streptococcus serum (Parke, Davis & Co., biological 2005) was given, 0.05 cc. into the skin at 12:05 p. m., a subcutaneous injection of 0.5 cc. at 12:07 and another of 1 cc. at 12:32 p. m.; an intramuscular injection of 0.5 cc. serum

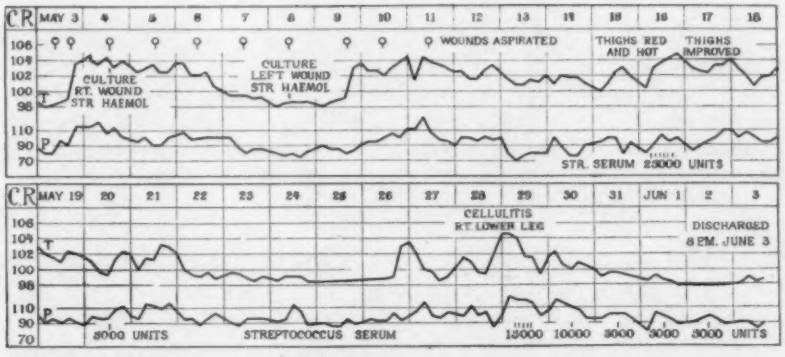

Chart 5 (case 66).—Abridged clinical record of C. R., a man aged 56, with infection of the wound following radical operation for carcinoma of the glans penis and inguinal metastasis. The favorable response to serum given on May 16 and May 20 was followed by a further extension of the inflammation on May 26, which promptly receded when further serum was given.

at 1:22 p. m., another of 1 cc. at 2:10 p. m. and another of 2 cc. at 3:12 p. m.; an intravenous injection of 0.1 cc. at 3:38 p. m., another of 0.2 cc. at 4:13 p. m., another of 0.3 cc. at 4:40 p. m. and another of 0.4 cc. at 4:55 p. m.—making a total of 6.05 cc. of serum for the day. All the doses except the first were diluted with a suitable amount of salt solution to facilitate injection through a fine needle. On the same day administration of sulfanilamide was started, 5 grains at 1 p. m. and 5 grains at 5 p. m. On January 30 the patient received 3 cc. of serum intravenously in four spaced injections and 15 grains of sulfanilamide by mouth. The serum was continued in daily amounts of 1 cc. from January 31 through February 9. The sulfanilamide was discontinued after February 1. Urticaria appeared on this day. The inflammation of the right arm had receded. The patient was discharged in good condition on February 19.

These 5 successful cases have been selected in order to illustrate the use of the serum under varied conditions. Case 32 presented an example

of temporary invasion of the blood stream from lesions on the hands, treated by subcutaneous injections of concentrated state serum to a total amount of 40,000 units. The patient recovered promptly from the infection and had a moderate serum rash ten days after the first injection of serum. The patient in case 73, a young woman desperately ill with streptococcic pneumonia, empyema and bacteremia, was treated with polyvalent streptococcus serum of Parke, Davis & Co., biological 2005, in large doses from February 10 to April 2, the total amount of serum used being 760 cc.; this treatment was augmented by multiple transfusions and surgical drainage of the pleural cavity. The patient in case 66, a man aged 56 with postoperative streptococcic infection, was treated with the regular (unconcentrated) serum of the New York state

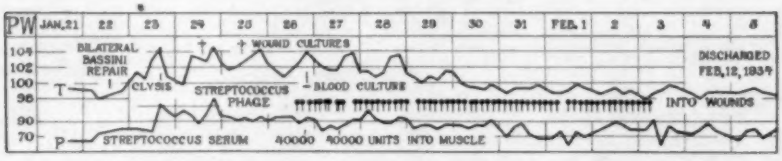

Chart 6 (case 36).—Abridged clinical record of a man aged 37, with streptococcic infection of the wound following repair of hernia. The serum was given by intramuscular injection, and a streptococcus bacteriophage was used for local application to the wound. The result was satisfactory.

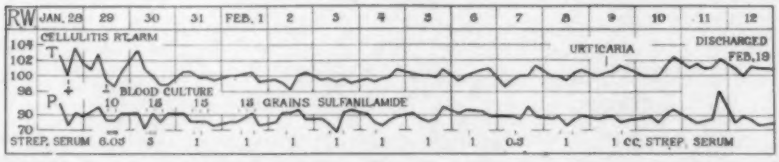

Chart 7 (case 86).—Abridged clinical record of R. W., with cellulitis of the right arm and bacteremia. Relatively small doses of sulfanilamide and of streptococcus serum were used, with very satisfactory results.

department of health. The first administration of the serum, on May 16, to a total of 25,000 units, was quickly followed by improvement of the patient's condition. An injection of 5,000 units of the serum was given on May 20. After a period of improvement there were a relapse and extension of the inflammation, and on May 29 more of the same serum was given in divided doses, to a total amount of 15,000 units. This was followed by 10,000 units on May 30 and 5,000 units on each of three days, May 31, June 1 and June 2. This time there was prompt improvement without further relapse. The patient in case 36 was a man aged 37, with postoperative streptococcic infection. On January 26 a streptococcus bacteriophage was applied to the wounds, and concentrated streptococcus serum (New York state), 40,000 units, was given intramuscularly on each of two days, January 26 and 27. The local bacteri-

ophage treatment was continued, and recovery was rapid. The patient in case 86 was treated with sulfanilamide in moderate doses for four days and with streptococcus serum (Parke, Davis & Co., biological 2005) on these four days and for eight days thereafter. She made a rapid recovery. We have, therefore, 1 patient who was treated with the concentrated streptococcus serum of the New York state department of health; 1 treated with the concentrated streptococcus serum, biological 2005, of Parke, Davis & Co.; a third treated with regular (unconcentrated) streptococcus serum of the New York state department of health; a fourth treated with concentrated streptococcus serum of the New York state department of health and local application of streptococcus bacteriophage; and a fifth treated with the streptococcus serum, biological 2005, of Parke, Davis & Co. supplemented with sulfanilamide. It is evident, therefore, that success may sometimes be achieved with any one of these three serum products, and it is probable that other serums would give similar results if used in the same way, in large doses continued over a sufficient period of time. It is also evident that there is no incompatibility between the serum and sulfanilamide or streptococcus bacteriophage employed simultaneously. There is even reason to hope that superior results may be obtained by the careful use of these agents in combination.

SUMMARY

Preliminary data are presented on 66 additional patients treated with streptococcus serum. We have previously reported the first 26 cases of our entire series of 92.

Severe streptococcus infection respects neither sex nor any age period. The youngest patient in our complete series was 19 days old and the oldest 80 years.

Of the 66 patients in the present group, 18 died. A brief account of each of the fatalities has been recited. There were 6 patients with diffuse bacterial meningitis and 2 with generalized peritonitis, types of disease in which the serum at present available does not offer much hope. In only 3 of the 18 cases was the effect of the serum really disappointing.

Five cases have been selected from the 48 in which the patients recovered, and these have been briefly presented as examples of treatment with three different preparations of streptococcus serum and of serum therapy in combination with multiple transfusions, with bacteriophage and with sulfanilamide, combinations which seem promising.

It is proposed to designate as the Hugh Young reaction the chill, sudden rise in temperature, diaphoresis and fall in temperature so often observed in the treatment of sepsis when an adequate amount of the antibacterial agent, be it a chemical, a bacteriophage or a serum, has been introduced into the blood stream to initiate the eradication of the infecting bacteria.

HEPATIC DAMAGE IN BILIARY DISEASE

ITS RELATION TO THE CONCENTRATION OF BILE ACIDS IN THE BILE

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It seems plausible that the decrease in the capacity of the liver to concentrate bile acids (taurocholic and glycocholic acids and their salts) in the bile should be an index to the amount of hepatic damage present. Bollman and Mann [1] have shown that bile acids are produced, destroyed and concentrated in and only by the liver. Smyth and Whipple,[2] as well as Bollman and Mann, have shown that small doses of substances known to be hepatotoxins, that is, chloroform, carbon tetrachloride and tetrachlorethylene, inhibit the function of the liver of the dog in producing and concentrating bile acids. Walters, Greene, and Frederickson [3] studied the constituents of the bile of a series of patients who had been operated on for biliary disease. They noticed that a decrease in the concentration of bile acids in the bile followed operations on the biliary system. Mann and two of us (McGowan and Bollman [4]) con-

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From the Division of Surgery of the Mayo Clinic (Drs. Gray, McGowan and Nettrour) and the Division of Experimental Medicine of the Mayo Foundation (Dr. Bollman).

1. Bollman, J. L., and Mann, F. C.: The Influence of the Liver in the Formation and Destruction of Bile Salts, Am. J. Physiol. **116**:214-224 (June) 1936.

2. Smyth, F. S., and Whipple, G. H.: Bile Salt Metabolism: I. Influence of Chloroform and Phosphorus on Bile Fistula Dogs; II Proteose and X-Ray Intoxication: Thyroid and Thyroxin, J. Biol. Chem. **59**:623-646 (April) 1924.

3. Walters, W.; Greene, C. H., and Frederickson, C. H.: The Composition of the Bile Following the Relief of Biliary Obstruction: Report of a Series of Illustrative Cases, Ann. Surg. **91**:686-693 (May) 1930.

4. McGowan, J. M.; Bollman, J. L., and Mann, F. C.: The Bile Acids in Icterus Produced by Toluylenediamine, J. Pharmacol. & Exper. Therap. **58**:305-311 (Nov.) 1936.

firmed these findings with dogs. Ravdin, Johnston, Riegel and Wright [5] have shown that bile salts are always absent from the hepatic bile after the common bile duct has been completely obstructed for a week or more and that the reappearance of such bile salts in the hepatic bile takes place only after a variable but considerable period.

Many patients with biliary disease have varying amounts of obstruction at the lower end of the common bile duct as a result of pancreatitis or spasm of the sphincter of Oddi, as has been demonstrated roentgenologically by Walters and Thiessen [6] and by means of studies of intrabiliary pressure by Butsch, Walters and one of us (McGowan).[7]

One would expect that improvement in hepatic function would occur as a result of the decompressing effect of T tube drainage. We attempted to correlate the reduction in concentration of bile acids with hepatic damage as evidenced by clinical or pathologic examination and to demonstrate improvement, if any, in hepatic function as a result of T tube drainage by frequent determinations of the concentration of bile acids in the bile.

METHODS OF STUDY

We studied 50 cases in which the common bile duct had been explored at the time of operation and in which prolonged biliary drainage by means of a T tube had been found necessary. The bile was collected in daily twenty-four hour specimens; it was thoroughly mixed, and a sample was placed in the refrigerator until the analysis was made. Bile acid concentration was determined according to the method of Gregory and Pascoe.[8] It was then attempted to correlate the bile acid concentration with the amount of clinical and pathologic evidence of hepatic damage.

The degree of hepatic damage was estimated from the history, from the report of tests for liver function and from the gross and microscopic appearance of the liver at the time of operation.

The chief factor in the history considered indicative of hepatic damage was jaundice. This is in accordance with the observations of

5. Ravdin, I. S.; Johnston, C. G.; Riegel, C., and Wright, S. L.: A Study of Human Liver Bile After Release of Common Duct Obstruction, J. Clin. Investigation **12**:659-672 (July) 1933.

6. Walters, W., and Thiessen, N. W.: Visual Methods of Studying the Physiology of the Common Bile Duct: I. The Problem of Pancreatitis and Sphincteritis, Proc. Staff Meet., Mayo Clin. **9**:772-775 (Dec. 19) 1934.

7. McGowan, J. M.; Butsch, W. L., and Walters, W.: Pressure in the Common Bile Duct of Man: Its Relation to Pain Following Cholecystectomy, J. A. M. A. **106**:2227-2230 (June 27) 1936.

8. Gregory, R., and Pascoe, T. A.: The Quantitative Determination of Bile Acids by Means of a New Color Reaction and Monochromatic Light, J. Biol. Chem. **83**:35-42 (July) 1929.

Snell,[9] made in a group of cases similar to ours, in which he showed that jaundice severe enough to produce a bilirubin content of 8.3 mg. per hundred cubic centimeters of serum was accompanied by evidence of impaired hepatic function.

The tests of function were the bromsulphalein, Takata-Ara, hippuric acid and galactose tolerance tests.

The degree of damage to the liver was classified as mild, moderate or severe. While we refer to some livers as "normal" or as having suffered no damage, all the patients studied had had biliary disease severe enough to require drainage of the common duct; probably none had escaped at least a minor degree of hepatic damage. In most instances the careful taking of the history gave an accurate index of the condition of the liver. In only 1 case in which the history indicated that hepatic damage was lacking did the test for retention of dye, the result which was graded 4, reveal what proved to be the true

TABLE 1.—*Relation of Hepatic Damage to Concentration of Bile Acids in Bile*

Damage to Liver as Classified by History	Cases	Tests of Hepatic Function Indicating Hepatic Damage, Jaundice (Twice or More), Percentage of Cases	Tests of Hepatic Function Indicating Hepatic Damage, Percentage of Cases	Hepatic Disease Noted by Surgeon, Percentage of Cases	Average Concentration of Bile Acids on Fifteenth Postoperative Day, Mg. per 100 Cc.
None ("normal")	21	5	0	20	1,840
Mild	11	45	27	43	1,165
Moderate	14	65	80	61	512
Severe	4	100	100	75	130

state of the liver. A history of jaundice on two occasions was followed by impairment of hepatic function. Patients classified as having severely damaged livers had jaundice at the time of admission, which had been present for periods varying from three weeks to one and a half years.

The duration of other complaints did not parallel the severity of the hepatic damage. Patients with normal livers had symptoms referable to the biliary system for an average of three years, whereas those with mildly, moderately and severely damaged livers had symptoms for an average of six, four and one-half and four years, respectively.

The gross appearance of the liver, while useful in classifying livers as normal, chronically inflamed or definitely cirrhotic, did not give accurate information with regard to the degree of physiologic change which was associated with these pathologic findings.

The percentage of each group of patients showing impairment of hepatic function increased progressively from the patients with mildly damaged livers to those with severely damaged livers.

9. Snell, A. M.: The Effects of Calculous Biliary Obstruction on the Structure and Functions of the Liver, Surg., Gynec. & Obst. **63**:596-602 (Nov.) 1936.

In 20 per cent of cases in which the liver was classified as normal and in 75 per cent of cases in which the damage was classified as severe there was gross pathologic evidence of hepatic disease at operation. This method of classifying hepatic damage, however, is more accurate than the figures indicate. For example, in the normal group the gross changes noted never indicated more severe damage than hepatitis of grade 1, whereas in the more severely damaged group hepatitis of grade 4, or cirrhosis, was frequently evident. When the evidence for hepatic damage was great, the function of that particular liver for concentrating bile acids was found to be low (figs. 1, 2 and 3).

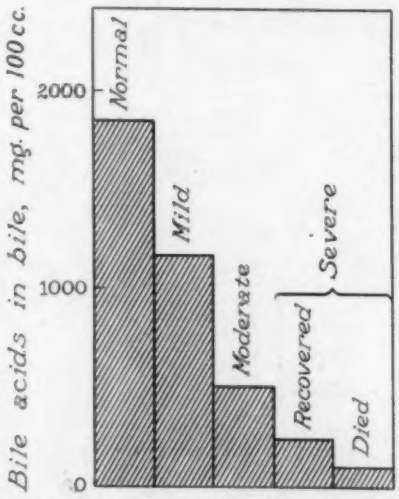

Fig. 1.—Average concentrations of bile acids in the bile of patients with normal livers and of those with clinical evidence of mild, moderate and severe hepatic damage, respectively.

After operation there was a progressive decrease in the concentration of bile acids in the bile of each individual patient. This reached a variable low level on the fourth day after the operation and then gradually rose to a fixed level on the fifteenth to the twenty-first day (fig. 4). Four patients showed improvement even after four weeks of biliary drainage.

Damaged livers did not completely regain their function of concentrating bile acids. This seems to indicate that there is a limit to the extent of recovery after injury. This limit is usually reached at the end of the second week, although improvement has continued much later. In 1 case in which the common bile duct had been com-

pletely obstructed by stricture there was a bile acid concentration of 33.8 mg. per hundred cubic centimeters in the first specimen, collected two hours after the operation. This value rose slowly and was continuing to rise even after one month, when it had reached 500 mg. per hundred cubic centimeters.

REPORT OF CASES

CASE 1.—*Normal liver.*

A man aged 56 complained of repeated attacks of biliary colic of one year's duration. He had never been jaundiced. Cholecystograms demonstrated a normally functioning gallbladder which contained stones. At operation the common duct

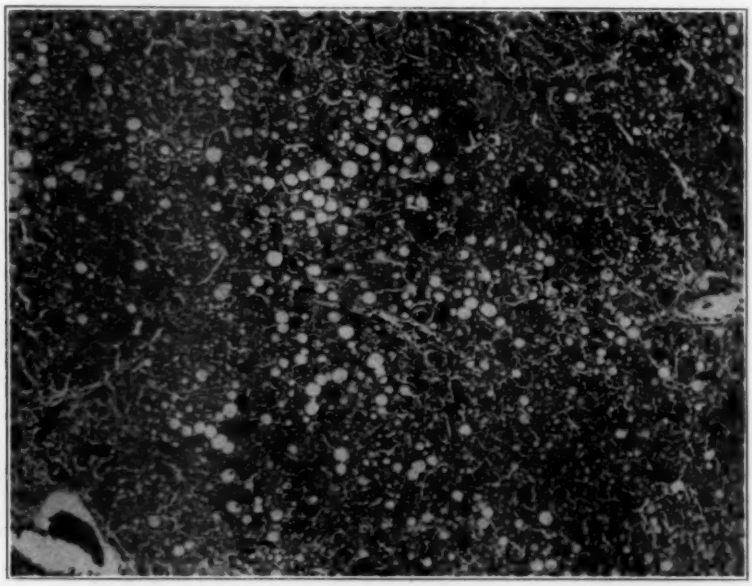

Fig. 2.—Section of liver graded clinically as moderately damaged. Biliary obstruction from carcinoma at the head of the pancreas was relieved by T tube drainage. The concentration of bile acids on the fifteenth day after the operation was 360 mg. per hundred cubic centimeters.

was seen to be enlarged to twice its normal size. It contained no stones. The gross appearance of the liver revealed hepatitis of grade 1. The only probable reason for hepatic damage in this case was back pressure on the liver, as indicated by the enlarged common duct and the biliary colic of one year's duration. The mildness of the symptoms, their short duration, the normally functioning gallbladder and the absence of jaundice and also of stones in the common duct would lead one to grade this liver as "near normal." The concentration of bile acids on the third day after the operation was 1,060 mg., and on the twelfth postoperative day 1,430 mg., per hundred cubic centimeters.

CASE 2.—*Severely damaged liver.*

A man aged 75 years had had jaundice with itching for one and a half years. The Takata-Ara test of liver function gave positive results. The hippuric acid test revealed excretion of only 0.64 Gm. of hippuric acid in the urine. The

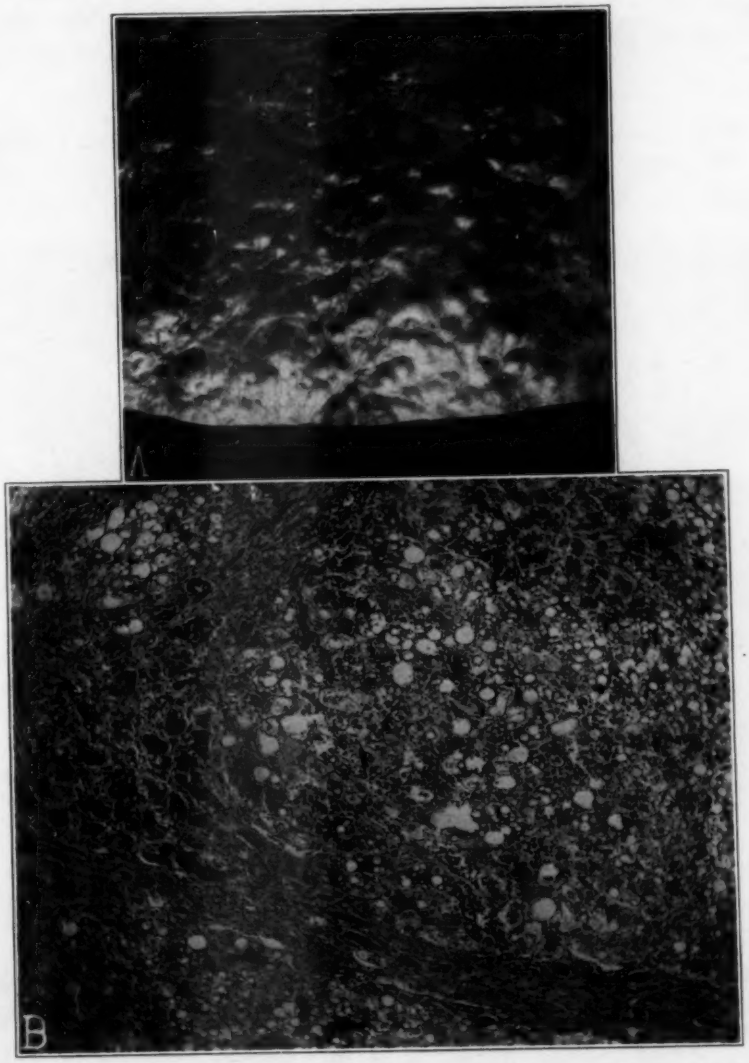

Fig. 3.—A severely damaged liver: *A*, in the gross, and *B*, in microscopic, appearance. Around the lobule is a broad band of fibrosis, mixed with which are scattered islands of parenchymal hepatic cells attempting to regenerate. The hepatic lobule itself consists of a framework with large empty spaces and little evidence of any parenchymal hepatic cells.

bilirubin content of the serum on admission was 8.3 mg. per hundred cubic centimeters; the protein content was 6.3 mg. per hundred cubic centimeters and the albumin-globulin ratio was 1:1.2. At operation a stone was found impacted in the ampulla of Vater. The liver revealed hobnail cirrhosis. The patient made a good recovery, and two weeks after operation choledochograms revealed a patent common duct. The concentration of bile acids on the fifteenth day after the operation was 224 mg. per hundred cubic centimeters.

COMMENT

Two patients with a concentration of bile acids in the bile constantly less than 100 mg. per hundred cubic centimeters died six and eight weeks, respectively, after operation (figs. 1 and 3). Two others, with

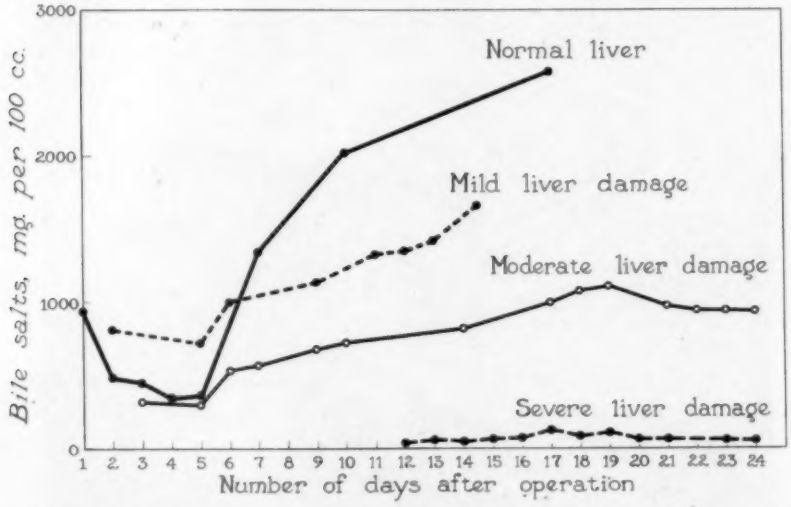
3000
2000
1000
0
Bile salts, mg. per 100 cc.
Normal liver
Mild liver damage
Moderate liver damage
Severe liver damage
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Number of days after operation

Fig. 4.—Concentrations of bile acids after operation in the bile of a patient with a normal liver and of patients with mildly, moderately and severely damaged livers.

a concentration of bile acids that remained slightly more than 200 mg. per hundred cubic centimeters for more than two weeks, slowly but completely recovered. These cases illustrate the prognostic value of the test. It would seem that when the amount of bile acids is constantly less than 200 mg. per hundred cubic centimeters the liver is severely damaged and the prognosis is grave.

The photomicrograph of the liver of the patient for whom the concentration of bile acids remained less than 100 mg. per hundred cubic centimeters showed destruction of hepatic cells in the center of the lobule and only a few parenchymal hepatic cells toward the periphery of the lobule (fig. 3). In contrast to this, figure 5 represents the

moderately damaged liver of a patient for whom the concentration of bile acids on the tenth day after the first operation, a year previously, was 690 mg. per hundred cubic centimeters and was 685 mg. per hundred cubic centimeters on the fifteenth day after an operation recently performed for stricture, at which time the specimen for biopsy was taken.

The clinical grading of hepatic damage can only be arbitrary, as it is impossible to say when a normal liver changes into a mildly damaged one. However, the evidence derived from a history of jaundice, from recognized tests of liver function and from the gross appearance of

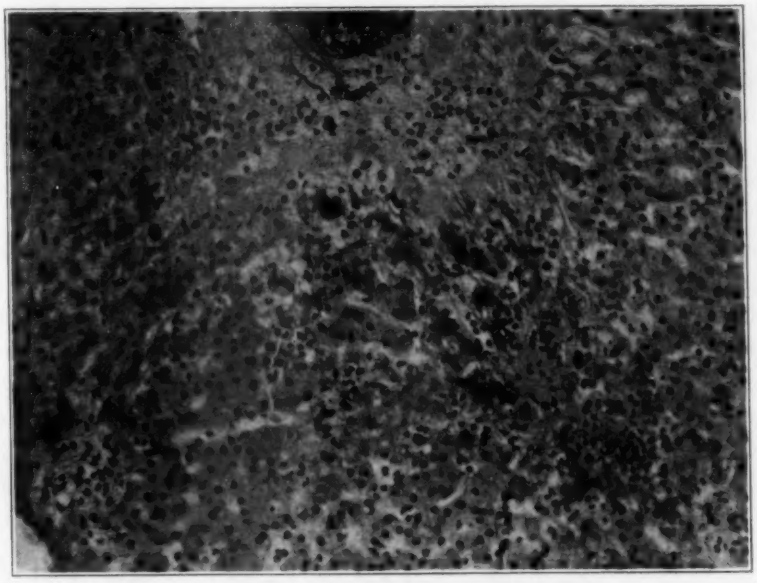

Fig. 5.—Biopsy specimen of a moderately damaged liver. The lower part represents fibrosis of the peripheral lobule and disappearance of parenchymal hepatic cells. Above is parenchymal hepatic tissue with groups of leukocytes indicating infection. The concentration of bile acids on the eleventh day after the operation was 685 mg. per hundred cubic centimeters.

the liver, while negligible for the normal liver, is 100 per cent indicative for the moderately damaged liver.

Paralleling this, the average concentration of bile acids in the bile on the fifteenth day after the operation for the normal liver is 1,840 mg. per hundred cubic centimeters and for the moderately damaged liver is 512 mg. We had only 1 case which proved an exception to this. Clinically the liver of the patient in this case was graded as normal, and grossly it suggested to the surgeon hepatitis of grade 1.

On the fifteenth day after the operation the concentration of bile acids was only 535 mg. per hundred cubic centimeters. However, it later rose to 1,820 mg.

This case illustrates what Smyth and Whipple have brought out in experimental studies on animals. They found that a definite decrease in concentration of the bile acids in bile may be present when neither gross nor microscopic evidence of hepatic damage is shown. The recovery of the ability of the liver to concentrate bile acids, which takes place after the postoperative depression, leads one to believe that such impairment in hepatic function may be only temporary. In cases in which there is gross clinical and pathologic evidence of hepatic damage complete recovery of the ability of the liver to concentrate bile acids does not occur.

The reason for the decrease in concentration of bile acids in the bile after operations on the common duct will need further investigation. The degree of this postoperative decrease in bile acid concentration is extremely variable and does not seem to have any relation to the degree of clinically demonstrable damage to the liver.

An interesting observation in these studies was that patients who had evidence of severe hepatic damage and bile acid concentrations greater than 200 mg. per hundred cubic centimeters on the seventh day after the operation made a slow recovery but apparently recovered almost as well as did those whose livers were apparently more nearly normal. This indicates that they had sufficient functioning hepatic cells to sustain healthy existence under these conditions. This amount of liver is probably represented by a concentration of bile acids greater than 200 mg. per hundred cubic centimeters. Concentrations greater than this and up to 3,000 mg. per hundred cubic centimeters may be spoken of as "liver reserve" (fig. 1).

The 2 patients who had concentrations of bile acids consistently less than 100 mg. per hundred cubic centimeters were up and about two weeks after operation and apart from lassitude, anorexia and persistently high bilirubin values showed no signs of grave hepatic damage (fig. 3).

The improvement in the function of the liver in concentrating bile acids during drainage of the common duct is striking and would seem to be a result of the decompressing effect of relieving tension in the biliary tree (fig. 4). It would seem wise, therefore, to prolong drainage of the common duct until the improvement in concentration of bile acids has ceased and until choledochograms and studies of intrabiliary pressure show the common duct to be unobstructed.

SUMMARY AND CONCLUSIONS

A clinical study was made of 50 cases in which drainage of the common bile duct was established by means of a T tube. The condition of the liver was estimated from the history, from the results of recognized tests of hepatic function and from the gross appearance of the liver at operation. The degree of hepatic damage thus determined was correlated with frequent determinations of the concentration of bile acids in the bile. Low concentrations of bile acids occurred in every case in which there was other evidence of hepatic damage. An inhibition in the function of the liver in concentrating bile acids occurred postoperatively. This inhibition was rapidly recovered from in cases in which the liver was clinically normal, but recovery was slower in those in which the liver had been damaged. A moderately damaged liver may continue to improve slowly even after a month of T tube drainage.

TECHNIC OF THE IVORY IMPLANT FOR CORRECTION OF SADDLE NOSE

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Much of the beauty of the face depends on the size and symmetry of the nose.[1] The saddle nose attracts the attention of even the most casual observer and is therefore "first of importance to be corrected."[2]

More than a hundred years ago Castle[3] wrote: "The bones of the nose, from their situation are much exposed to fractures. The fragments are sometimes not deranged; but, most frequently they are depressed." The same thought has been expressed by me in a recent article.[4] Trauma is the most common cause of saddle nose.

Contrary to the opinions of some,[5] I believe with others[6] that animal (elephant) ivory offers the ideal implant for the correction of such deformities. Cork[7] has been employed, although reports of the results after a period of years are not to be found in the literature. Since the chemical composition of cork is purely vegetable the probability of retention of the implant is always uncertain.

Autoplastic materials (bone and cartilage) often produce an abnormal midline ridge, due sometimes to narrowness of the graft but most frequently to absorption. A nose with such a deformity has been referred to as a "keel nose."

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1. Warren, J. C., and Gould, A. P.: International Text-Book of Surgery, Philadelphia, W. B. Saunders Company, 1900, vol. 2, p. 77.

2. Hays, H.: Diseases of the Ear, Nose and Throat, Philadelphia, F. A. Davis Company, 1925, p. 522.

3. Castle, T.: A Manual of Surgery, ed. 4, London, E. Cox, 1831, p. 379.

4. Wolfe, M. M.: Etiology of the Saddle Nose, Ann. Otol., Rhin. & Laryng. **44**:504-509 (June) 1937.

5. Sheehan, J. E.: Plastic Surgery of the Nose, New York, Paul B. Hoeber, 1925, p. 8. Carter, W. W.: Correction of Nasal Deformities by Plastic Methods and by Transplantation of Bone and Cartilage, Internat. J. Orthodontia **19**:1012-1016 (Oct.) 1933.

6. Maliniak, J.: The Use of Ivory in Rhinoplasty, Arch. Otolaryng. **1**:599-611 (June) 1925. Salinger, S.: Ivory Implants for Saddle Nose: Results in Fifty Cases, Ann. Otol., Rhin. & Laryng. **40**:801-808 (Sept.) 1931.

7. Priselkov, P. V.: The Use of Cork in the Surgical Treatment of Saddle Nose, Vrach. gaz. **34**:534-536, 1930. Dahmann, H.: Cork as a Plastic Material for the Raising of "Saddle Noses," Ztschr. f. Laryng., Rhin., Otol. **20**:451-457 (March) 1931.

The two stage operation for the correction of saddle nose has been previously described.[8] In this contribution the one stage operation will be discussed in detail.

Ivory has been employed for almost twenty-five years. It has stood the test of time; it retains its original shape and size, and it possesses the other attributes essential for this type of operation.

For successful results in the correction of a saddle nose, attention to minute details is of paramount importance.

First, one must be absolutely certain that one has genuine elephant ivory. Ivory from young elephants appears to be better conditioned physiologically than does that from old elephants. When treated with concentrated sulfuric acid for fifteen minutes genuine ivory is not affected, while vegetable ivory and walrus tusk[9] are stained rose color; the tint disappears if the substance is washed in water. The latter two substances are not to be used on account of their irritating qualities and on account of the fact that they are not retained by the host.

A cast of the face is made in all cases of saddle nose. An impression (regular dental impression plaster) is made of the patient's face from the midforehead to and including the upper lip. This permits the patient to breathe through the mouth. To facilitate the removal of the impression, the face is greased with olive oil, heavy petrolatum is applied to cover the eyebrows and eyelashes, and tiny pieces of cotton soaked in olive oil are inserted in both nostrils. When the impression begins to harden it is removed by being raised at the forehead section, with a forward and downward motion. The inner surface of the impression is painted with a thin layer of (dental) shellac, which dries in about fifteen minutes. It is then treated with a thin coat of sandarac, which requires about thirty minutes for drying. The impression is next soaked in cold water for about three to five minutes (until bubbling ceases). This soaking replaces the moisture lost during the hardening (crystallization) of the plaster. The impression is not to be dried after soaking. Modeling plaster is then poured into the impression, and the cast is inverted. As soon as the cast begins to harden, the edges are trimmed with an ordinary pocket knife to discover the line of demarcation, and by a wedging motion the two are separated (fig. 1 *A*). Personally, I prefer "artificial stone" for the production of the model; it withstands repeated fittings of the ivory much better than does plaster of paris.

A suitable piece of ivory having been selected, the dorsum of the nose of the cast is smeared with lipstick. The ivory is placed on the

8. Wolfe, M. M.: Plastic Surgery of the Saddle Nose, Laryngoscope **43**: 897-904 (Nov.) 1933.

9. Watkins, A. B. K.: Notes on Plastic Surgery, J. Laryng. & Otol. **48**:809-820 (Dec.) 1933.

nose, and wherever the lipstick leaves its imprint the ivory is carved. For the carving I employ a rotary motor with carborundum wheels, one flat and the other round. After repeated fitting and carving, the under surface when completed will fit the depression (saddle deformity) with the accuracy of a dental inlay. The superior surface, or what is subsequently to become the new dorsum of the nose, is then carved to a height and width equal to the depth and width of the deformity. It is then drilled with tiny holes. This lightens the implant and permits fibrous bands to grow into the ivory, holding it more securely in position. In every case two pieces of ivory are carved; one to fit the depression

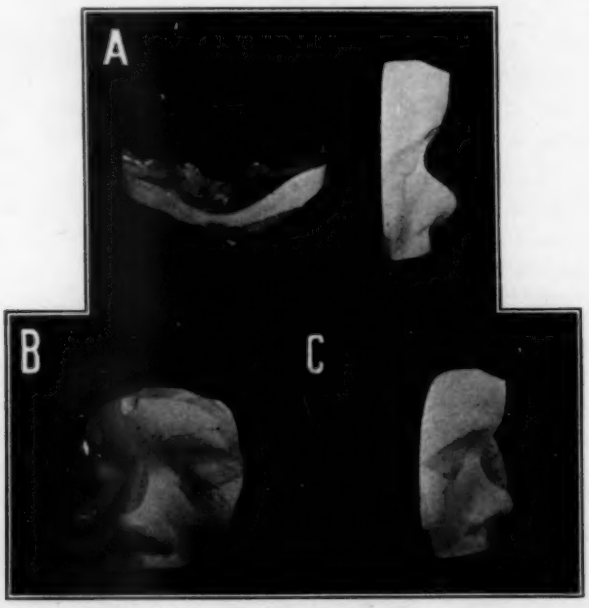

Fig. 1.—*A*, photograph showing the cast after its removal from the impression taken of the patient's face. *B*, ivory implant accurately carved to fit the saddle deformity. *C*, oversized implant most commonly employed for the severe types of saddle nose.

accurately (fig. 1 *B*) and the other slightly oversized (fig. 1 *C*). This is to allow for the thickness of the skin and to insure a better cosmetic result by the trying of two implants. The implants are scrubbed with soap and water to cleanse them and to remove the lipstick. The sharp edges are then made perfectly smooth with a fine sandpaper disk, a dental engine being employed. This is just as important as the actual fit of the implant. A sharp edge is likely to irritate locally, produce a serous exudate and eventuate in expulsion of the implant. Then, too, as in the case of a mild injury, a sharp edge will traumatize the

fibrous enveloping capsule; this will also result in loss of the ivory. All such complications may be entirely eliminated if the implant is properly carved, accurately fitted and smooth on all surfaces.

The implants are wrapped in gauze and sterilized by boiling. The water must be cold; the temperature should be increased slowly. If the temperature of the water is raised too rapidly or if the implant is placed in boiling water, the sudden external expansion of the ivory will cause it to crack, and it then becomes useless. The nurse is instructed to boil the implant for twelve minutes in distilled water. Prolonged boiling has a tendency to remove some of the constituent salts, thereby changing the chemical composition of the ivory and decreasing its resistance to eventual expulsion. Moreover, it is essential to retain all the chemical components of ivory in nearly the original state if the biologic characteristics of the substance are to be preserved.

Many types of outside incision are employed for the insertion of implants. Among them are the superciliary, glabellar, nasion, canthal and columellar incisions, which result in an "almost invisible scar." My own preference has always been to employ the intranasal incision so that no scars are visible.

The preliminary preparation consists of closely clipping the hair in the nostrils with special blunt-pointed scissors with a convex back; this prevents nicking the skin. Crusts and intranasal débris are removed with hydrogen peroxide. The patient washes the face with soap and water to remove grease and cosmetics. The nose is then packed with a 1:8,000 dilution of mercurophen a half-hour before operation. Such a simple preoperative routine has proved to be not only exceedingly effectual but less complicated and less traumatizing than douches for the nose and the use of various antiseptics and germicides.

One hour before operation the patient is given a mild sedative. Morphine alone or in combination with atropine is never employed, on account of the short duration of the operation and the possibility of an idiosyncrasy.

The patient's face is finally prepared on the operating table; this preparation consists of cleansing with alcohol and then with tincture of metaphen in a dilution of 1:200 (untinted), which is removed with alcohol. The nasal packing is removed, the face is draped and the nose is anesthetized. General anesthesia should not be employed in rhinoplastic operations. The postoperative nausea and vomiting incident thereto obviously invite infection. Infiltration hydrochloride anesthesia is the method of choice; a 1 per cent solution of procaine hydrochloride with epinephrine is administered intranasally to the sides and dorsum of the nose.

For insertion of the implant an incision is made within the left vestibule at the inferior border of the triangular cartilage (fig. 2). The length of the incision depends on the size of the implant to be inserted. By blunt dissection with the Joseph comma knife, sufficient skin is separated overlying the dorsal and lateral walls of the nose to produce a pocket for the reception of the ivory. As a general rule there is little bleeding from this dermal separation. After several trials have been made, the implant which best fits the deformity is permitted to remain. The implant must never be touched; it is handled entirely with instruments. The skin overlying the implant must not be on a stretch, as any tension may alter the nutritional supply of the dorsal skin and may defeat the operation. The implant having been adjusted, three strips of adhesive tape are placed over the nose; this constitutes the

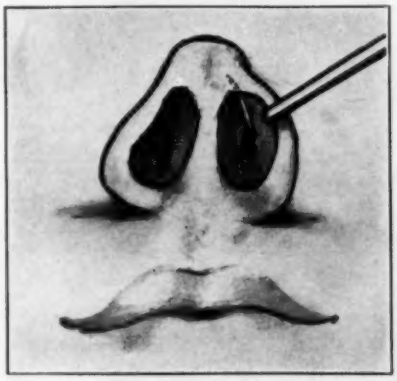

Fig. 2.—Sketch illustrating the incision made within the left vestibule at the inferior border of the triangular cartilage. If the surgeon is left handed, the incision is made on the opposite side. One incision is sufficient.

external dressing. A small piece of gauze treated with petrolatum is placed in the nostril against the line of incision, to keep the wound moist and permit free drainage. Suturing of the line of incision as done by some surgeons not only prevents free drainage but is likely to produce a hematoma, thus inviting infection. The patient is kept quiet in bed for three days in the semireclining position. The petrolatum gauze pack only is changed daily. After the third day the three external strips of adhesive tape are removed, and no further dressings or applications are necessary. By this time the implant is held in position by the overlying skin, which has contracted, and by the accurate fit of the ivory to the dorsum of the nose. The patient rarely complains of any postoperative pain, and the swelling completely subsides in about five days. If the implant has been retained beyond the first week and there are no visible

differences in the appearance of the new nose, the ivory will usually remain in situ indefinitely.

Slight injuries to the nose are usually well tolerated. Even though the trauma is sufficient to produce a local reaction the ivory will remain in place if the fibrous capsule is not disturbed. A severe blow, however, rupturing the fibrous envelop will produce a marked reaction with all the signs and symptoms of acute inflammation and with subsequent expulsion of the implant either at the side of the nasion or through the nasal mucosa. At the first sign of any irritation the implant should be removed via the original incision, and the nose should be drained with a rubber dam for twenty-four to forty-eight hours. When regeneration is completed a new implant may be inserted after a lapse of from six to eight weeks. It is almost superfluous to add that plastic corrections should never be attempted in the presence of any active pathologic

Fig. 3.—Photographs showing result of the implantation. The picture at the left was taken before the operation; that on the right, after the operation.

process in the nose and never before the patient reaches the age of 17, at which time the nose has attained its full growth.

SUMMARY

External incisions of the nose, regardless of their location, always result in scarring, while incisions about the tip have a tendency to destroy its natural contour. The accepted intranasal incision not only is easier of approach but never results in any scarring. It is time that all external incisions for practically all types of nasal corrections were relegated to the scrap heap of plastic operations.

Properly selected ivory taken from a young elephant and carefully carved is of preeminent importance for a good cosmetic result. The overlying skin should never be subjected to any tension. In doubtful cases, in which the dorsal skin is rather firmly attached (as the result of

Fig. 4.—Photographs showing the result of the implantation. The picture on the left was taken before the operation; that on the right, after the operation.

Fig. 5.—Photographs of a third patient, taken before and after the implantation.

Fig. 6.—Photographs of a fourth patient, taken before and after the implantation.

severe injury or infection), it is better to employ a rather small implant, achieving at least some improvement, than to take the risk of complete failure caused by stretching the skin.

The insertion of the implant is a simple procedure and is quickly accomplished, which is gratifying to the patient. The insertion of an autogenous graft is always attended with some danger; in addition such an operation requires general anesthesia.

The encapsulation of the implant with fibrous tissue seems to be uniform and never distorts the end result. It is known that autogenous implants do become absorbed irregularly and result in various distortions. If the patient is apparently in good health, the nasal orifices free from infection, asepsis and antisepsis rigidly observed, properly carved elephant ivory employed and careful technic used one should have no hesitancy in using this method for the correction of saddle nose.

Any implant which is easily procured, readily prepared, quickly inserted, resistant to infection and well tolerated by the tissues possesses merit of distinction. Elephant ivory is an organic substance the chemical composition of which is similar to that of human bone. This accounts for its nonirritating effect and for the fact that it is not acted on as a foreign body. Moreover, elephant ivory never changes its shape or becomes absorbed. For these reasons, elephant ivory has definitely established its reputation as the ideal implant for the correction of saddle nose.

The Widener Building.

DUODENAL RUPTURES

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Retroperitoneal duodenal tears occupy a particular place among subcutaneous intestinal ruptures of traumatic origin. The integrity of the peritoneum creates diagnostic difficulties during the first hours after the trauma.

According to the statistical reports of Kenn,[1] only 9 of 138 patients with retroperitoneal and intraperitoneal duodenal ruptures recovered. Retroperitoneal ruptures are often overlooked during laparotomy (Gibe[2]). The presence of retroperitoneal hematoma, emphysema or a green spot on the parietal peritoneum makes the surgeon suspect ruptures of the retroperitoneal hollow organs. The diagnosis is most difficult in cases in which there are injuries of other viscera. In case of blunt trauma to the abdomen, after manipulation of the intestine and other internal organs has been completed the duodenum should be investigated if there are evidences of retroperitoneal hematoma, emphysema or a green spot on the parietal peritoneum. The location of the lower horizontal part of the duodenum on the fixed spinal column in cases of acute trauma predisposes to ruptures of that portion of the duodenum. One may suppose that at the moment of trauma the duodenum represents a bag filled with gas and hermetically closed. On one side the exit from the duodenum is closed by the contracted pylorus, on the other it is closed by the superior mesenteric artery and the root of the mesentery pressing on the flexura duodenojejunalis at the moment of the trauma. The volume of gas, diminishing in the moment of impact, increases the compression, and the intestine bursts. Some particular features of the clinical picture of duodenal tears draw attention in my case, which seem worthy of reporting.

REPORT OF A CASE

Mr. K., a man aged 30, was admitted to the hospital because of a trauma of the abdomen. He had been pressed against a wall by a truck. There was acute abdominal pain. The pulse rate was 48. Cold sweat and shock were present. Palpation established a more or less intense strain of the muscles in

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From the Surgical Clinic, Prof. Dr. Med. M. A. Kimbarowsky, Director.

1. Kenn, cited by Mondor, H.: Diagnostics urgents: Abdomen, ed. 2, Paris, Masson & Cie, 1933, vol. 1.

2. Gibe, cited by Mondor, H.: Diagnostic surgents: Abdomen, ed. 2, Paris, Masson & Cie, 1933, vol. 1.

the right half of the abdomen. There was tympanic resonance in the whole right half of the abdomen, the zone of the tympany passing to the external surface of the lumbar region. Hepatic dulness was maintained. The borders of the lungs and heart were normal. Six hours after injury a laparotomy was performed in the midline. Small multiple tears of the ascending colon and the transverse colon about the liver were detected, as well as multiple ruptures of the seromuscular coat of the ascending colon. Some accumulation of blood in the lower part of the peritoneal cavity and in the Douglas pouch was noted. There was marked retroperitoneal emphysema. A retroperitoneal rupture of the ascending colon was suspected. The large intestine was mobilized. In the retroperitoneal space a hematoma of considerable size was detected. The posterior wall of the ascending colon was traumatized and was infiltrated with blood. A rupture 4 cm. in length was revealed in the retroperitoneal portion of the duodenum at the site of passage of the descending part of the duodenum into the lower, horizontal part. Resection of the mobilized part of the large intestine, followed by an end to side ileocolostomy, was performed. The duodenal tear was closed with a double line of sutures. Careful peritonization at the site of rupture was accomplished and the omentum was sutured to the line of peritoneal sutures. The abdominal wound was closed.

The postoperative course was aggravated by bilateral lobar pneumonia with an abscess of the right lung. On the sixteenth day, in spite of the absence of any evidence of infection in the peritoneal cavity and in the right lumbar region, a disruption of the wound in its lower half occurred, with eventration of the intestinal loop, which had been well delimited from the free peritoneal cavity by adhesions. One day later a fistula of the transverse colon developed. There were increased symptoms of disease of the lungs; abscess and gangrene of the right lung were present. The patient died on the twenty-first day after injury.

Autopsy.—Myocardial degeneration and induration of the inferior lobe of the left lung (lobar pneumonia) were observed. The right lung was edematous and infiltrated. The upper part of the inferior lobe was occupied by the abscess cavity, the walls of which consisted of gangrenous tissue. There were multiple loose adhesions between loops of small intestine. An eventrated loop of the ileum and a part of the colon were well delimited from the free peritoneal cavity. The duodenal suture was in good condition. In the region of suture of the parietal peritoneum an inflammatory infiltration without suppuration was noted. The anastomosis and the stump of the transverse colon were in good condition. Three centimeters above the anastomosis and 5 cm. from the stump on the anterior wall of the transverse colon a fistula 0.5 cm. in diameter was observed. Between the loop of the small intestine and the anterior peritoneal wall at the left a well encapsulated round abscess 1 cm. in diameter was seen. The subdiaphragmatic and the Douglas pouch showed no unusual conditions.

Attention must be drawn to the fact that, in spite of the presence of traumatic injuries of the large intestine along with the retroperitoneal duodenal rupture, peritoneal symptoms were not sharply marked; now and again they almost disappeared. As the condition of the patient was very poor and caused me to suspect a rupture of the hollow or parenchymatous organ, a laparotomy was done. Particular attention has been drawn to the symptom of extension of the zone of tympanic resonance to the right lumbar region as a result of the retroperitoneal

emphysema. The green spot on the parietal peritoneum, insisted on by Lafitte,[3] was not observed. The extreme emphysema forced me to look for perforation in the colon and the duodenum retroperitoneally.

The case demonstrates the necessity of a careful investigation of the retroperitoneal region of the duodenum in the presence of retroperitoneal emphysema.

3. Lafitte, H.: Arch. franço-belges de chir. **34**:117 (Feb.) 1934.

MAGGOT THERAPY FOR HEMATOGENOUS OSTEOMYELITIS OF THE TIBIA

STEPHEN MADDOCK, M.D.

WITH THE ASSISTANCE OF

DOROTHY JENSEN, A.B.

BOSTON

When Baer [1] announced in 1929 that he was using live blowfly maggots to treat osteomyelitis, there was a decided wave of interest throughout the United States. Many surgeons began using the method, and enthusiastic reports [2] appeared in the literature. After this preliminary wave of enthusiasm the use of maggots became more limited, but certain clinics have continued the practice. At present it is difficult to evaluate the method from the literature or to determine how widely it is used.

The purpose of this communication is to present in some detail a series of 29 cases in which hematogenous osteomyelitis of the tibia has been treated during the past seven years and which have been followed up to the time of writing. Most of the patients had been operated on by other surgeons, and treatment with maggots was begun after a period of antecedent treatment. Any additional operations were performed by me. In most instances the preliminary procedure was of the Orr [3] type. The series lacked uniformity of operative treatment but by the same token was representative of various types of surgical technic and experience, so that the results are comparable with those which might be expected in private practice.

From the Osteomyelitis Clinic, the Surgical Research Laboratory and the Fifth (Harvard) Surgical Service of the Boston City Hospital.

Dr. Frederic J. Cotton originally suggested the use of maggots and was instrumental in obtaining technical assistance in producing them. Dr. Otto J. Hermann, chief of the orthopedic service, assisted in this work. Drs. A. R. Kimpton, R. C. Cochrane, J. H. Shortell, W. R. Morrison, C. C. Lund, J. H. Burnett, T. H. Peterson, R. H. Aldrich, L. R. Dretler, C. H. Bradford and P. W. Shannon, of the Boston City Hospital staff, referred cases observed in this report.

1. Baer, W. S., in discussion on Bitting, N. D.: Acute Osteomyelitis and Complications, South. M. J. **22**:580-583 (June) 1929.

2. Robinson, W.: Progress of Maggot Therapy, Am. J. Surg. **29**:67-71 (July) 1935.

3. Orr, H. W.: New Method of Treatment of Chronic Infections Involving Bone, Nebraska M. J. **8**:50-52 (Feb.) 1923.

The literature has grown so voluminous that it is impossible to review it here. The reader is referred to the bibliography compiled by Robinson.[4]

OPERATIVE PROCEDURE

The preliminary operative treatment of the subacute condition was essentially that described by Orr.[5] In some instances several operations had been performed before maggot treatment was begun. Patients with chronic osteomyelitis who came directly to me were usually treated with maggots for from two to four weeks before any operation was performed. A few of the lesions healed without operative intervention. When operation proved necessary, all infected bone and scar tissue was removed, a base of viable bone being left. The cavity was packed with petrolatum gauze, and a cast was applied. In all the cases of bone abscess (Brodie[5]) described here the lesion had been opened wide and packed with petrolatum gauze by another surgeon before the patient was referred to me for maggot treatment.

METHODS

The production and sterilization of maggots have been described so carefully by several writers[6] that no mention need be made of this process. All the methods are essentially the same, but the latest technic of Robinson[6c] has proved the simplest and most satisfactory.

Maggot Therapy.—Approximately one week after the operation in cases of chronic osteomyelitis or four weeks or more in cases of acute disease the petrolatum gauze packing is removed. Any accumulation of pus is sponged out, and the bleeding is controlled by pressure. In order to establish maggots promptly, the wound is rendered alkaline by irrigation with a 0.25 per cent suspension of calcium carbonate.[7] After irrigation the wound is gently sponged dry, and enough maggots are inserted to cover its surface. The exact number in any given case can be determined only by experience and experiment. The skin is protected with some waterproof material in order to prevent its being digested by the enzymes in the excreta of the maggots. After the implantation the depths of the wound are packed lightly with fluffed gauze, and the whole is covered

4. Robinson, W.: Literature Relating to the Use of Maggots in the Treatment of Suppurative Infections, Bulletin 310, United States Department of Agriculture, Bureau of Entomology, 1934.

5. Brodie, B.: Lecture on Abscess of the Tibia, London M. Gaz. **36**:1399-1403, 1845.

6. (*a*) Child, F. S., and Roberts, E. F.: The Treatment of Chronic Osteomyelitis with Live Maggots, New York State J. Med. **31**:937-943 (Aug. 1) 1931. (*b*) Livingston, S. K.: Maggots in the Treatment of Chronic Osteomyelitis, Infected Wounds and Compound Fractures, Surg., Gynec. & Obst. **54**:702-706 (April) 1932. (*c*) Robinson, W.: Improved Methods in the Culture of Sterile Maggots for Surgical Use, J. Lab. & Clin. Med. **20**:77-85 (Oct.) 1934.

7. Stewart, M. A.: A New Treatment of Osteomyelitis, Surg., Gynec. & Obst. **58**:155-165 (Feb.) 1934.

with gauze and cellucotton pads. This type of dressing is much simpler than any of the cages which have been recommended and has the great advantage of keeping the wound from becoming filled with pools of pus in which the maggots will drown.

Contrary to general practice, the dressings are usually changed daily. This keeps the skin in good condition and adds materially to the comfort of the patient. It is possible to remove some of the maggots when they are obviously crowding the wound and causing pain or to replace them if they have failed to survive.

Clinical Course.—One may expect the wound to put forth healthy granulation tissue within from two to four weeks after the beginning of the treatment. Small chips and lumps of cancellous bone make their appearance during this period and can be lifted out with forceps. Occasionally the edges of the osseous defect and small islands of firmly attached bone will fail to granulate. Such areas are insensitive and can be removed with rongeurs or a gouge, without anesthesia. After their removal, bleeding is stopped by pressure, and treatment with maggots can be continued at once or on the following day.

If during the course of treatment the wound fails to make reasonable progress, roentgenograms will often reveal some deep area of involvement which has been overlooked at operation. Insertion of a probe in a suggestive depression in the wound while the films are being taken often serves to point out the offending bone. Patients with such involvement should not be reoperated on at once if the wound is making satisfactory progress. Considerable judgment is required to determine the best course to pursue. Many such apparent sequestrums revascularize and are incorporated into the new bone. Others become more sharply demarcated in time and can be removed mechanically without anesthesia.

Maggots need not be left in the wound until complete epithelization has occurred, but the question of the proper moment to discontinue their use is at times difficult to decide. In general, the best criteria are a healthy looking wound and a roentgenogram showing no abnormality. It is my custom to remove maggots at this stage and substitute urea crystals [8] or dry dextrose. Some wounds regress after this change, and it is necessary to return to treatment with maggots. Others show steady improvement, and the skin begins to grow in from the edges; in such the lesions should be prepared for skin grafts. This procedure not only hastens closure but produces skin over the affected area which is better able to withstand possible future injury.

Patients are allowed to sit up as a routine as long as they remain afebrile. Crutches are issued as soon as the wound becomes well covered with granulations, and their use is continued until complete closure has occurred. When involvement of the legs is bilateral, walking is permitted as soon as the wound on one leg is closed. Healing of the skin sometimes has been delayed by allowing the patient to hold the leg in a

8. Holder, H. G., and MacKay, E. M.: The Use of Urea in the Treatment of Infected Wounds, J. A. M. A. **108**: 1167-1169 (April 3) 1937.

dependent position; this results in venous congestion. The delay required for correct healing is more than offset by the advantage of early return to work. Patients are kept in the hospital only until it becomes probable that no further operations on the bone will be necessary. They are then sent home with directions to return to the clinic for treatment.

In some cases treatment with maggots was not begun until after the patient was discharged from the hospital. It was found feasible to use the treatment for ambulatory patients, with three dressings per week. Such patients were occasionally readmitted to the hospital for sequestrectomy or skin grafts.

After closure has occurred the patient is told to return at intervals of from one to three months for clinical and roentgen examination. The intervals are gradually lengthened, but each patient is seen every six months.

Death of Maggots in Wounds.—In all of his papers Baer referred to the phenomenon of death and dissolution of maggots, which occurred in each case toward the end of the healing process. He regarded this as due to acquired immunity of the patient to maggots. Livingston and Prince [9] explained it as being due to the development of a higher p_H and to the production of their "active principle." During the present investigation the dying out of maggots has never been observed. Late in the treatment the maggots do not grow rapidly, and many doubtless die of inanition, but they have never been seen to dissolve in the wound. That the patient does not acquire immunity to maggots has been amply demonstrated in numerous cases in which treatment was stopped for periods varying from one week to almost a year.[10] On resumption of treatment there was no evidence of inability of the maggots to survive. Several patients have had multiple lesions which healed at different times, yet the last wound in each case continued to support maggots as long as they were used. A few patients have returned with localized infections in the overlying soft parts. These have often been treated with maggots, and it has never been found difficult to establish or maintain the larvae. It would seem, therefore, that the death of maggots is probably caused by starvation, escape from the wound or low viability of the culture.

RESULTS

The results of this study are given in table 1 and summarized in table 2. The 29 cases are grouped under appropriate headings and

9 Livingston, S. K., and Prince, L. H.: The Treatment of Chronic Osteomyelitis with Special Reference to the Use of the Maggot Active Principle, J. A. M. A. **98**:1143-1149 (April 2) 1932.

10. Maddock, S., and Jensen, D.: The Treatment of Septic Compound Fractures of the Tibia with Maggots, New England J. Med. **217**:123-129 (July 22) 1937.

numbered in each group according to the time at which maggot therapy was started. The series seems to be divisible naturally into three categories, the first including cases of subacute osteomyelitis; the second, cases of chronic osteomyelitis, and the third, cases of abscess of the bone (Brodie [5]). There was no case of true acute osteomyelitis in the series, since treatment with maggots was not started until the patient had passed through the critical febrile phase of the illness.

TABLE 1.—*Results of Maggot Treatment*

Case	Age	Date of Onset	Premaggot Operation	Maggot Therapy Started	Maggot Therapy Stopped	Discharge from Hospital	Result	
				Subacute Hematogenous Osteomyelitis				
1	14	2/14/31	8/ 7/31	8/21/31	11/ 8/31 12/25/31	12/25/31	Closed.....	11/19/31 R 2/16/32 L
2	9	8/12/31	8/21/31	8/29/31	9/25/31	11/ 6/31	Closed.....	8/12/32
3	7	8/29/31	9/ 2/31	2/10/32	4/ 6/32	5/ 5/32	Closed.....	12/12/32
4	5	8/ 9/31	1/21/32	2/14/32	3/13/32	4/28/32	Closed.....	10/15/32
5	11	5/25/32	6/12/32	6/29/32	7/31/32	2/23/33	Amputation..	11/11/32
6	16	5/25/32	6/ 3/32	6/12/32	9/21/32	2/12/33	Amputation..	2/12/33
7	14	12/10/32	4/18/33	5/16/33	10/14/33	7/ 3/32	Closed.....	10/16/33
8	14	8/30/32	11/15/32	2/ 3/33	2/ 8/34	4/14/33	Closed.....	5/ 1/34
9	13	2/12/34	3/18/34	4/ 2/34	9/ 4/34	5/28/34	Closed.....	1/11/35
10	14	7/31/34	8/ 4/34	8/27/34	11/12/35	10/31/34	Closed.....	1/25/36
11	12	2/17/35	2/18/35	3/26/35	2/ 7/36	12/ 5/35	Closed.....	2/23/37
12	8	8/ 3/34	8/ 4/34	4/ 9/35	10/23/35	10/ 5/35	Closed.....	1/22/36
13	14	10/15/35	10/18/35	12/11/35	2/22/36	11/22/35	Closed.....	12/14/36
14	9	10/10/35	10/14/35	1/ 2/36	2/22/36	12/15/35	Closed.....	6/28/36
15	9	8/ 9/35	11/16/35	1/ 7/36	3/ 2/36	12/18/35	Closed.....	5/12/37
16	11	10/12/35	10/20/35	1/ 7/36	2/22/36	4/19/36	Closed.....	4/19/36
17	15	7/31/36	11/24/36	1/ 5/37	3/10/37	6/ 3/37	Closed.....	3/17/37 L 6/ 1/37 R
				Chronic Hematogenous Osteomyelitis				
18	53	1889	1/14/31	2/ 6/31	5/30/31	6/ 4/31	Closed.....	3/12/35
19	30	1912		11/26/32	12/29/32	6/12/33	Closed.....	10/ 1/33
20	55	1912		12/19/32	1/27/33	4/26/33	Lost	
21	19	1929	4/11/33	5/ 6/33	6/26/33	8/16/33	Lost	
22	49	1895	6/14/34	6/18/34	7/20/34	8/18/34	Closed.....	9/ 2/34
23	10	1933	5/24/33	12/ 9/35	1/ 2/36	6/21/33	Closed.....	2/20/36
24	51	1900	11/29/35	1/ 2/36	2/12/36	12/28/35	Closed.....	9/25/36
				Brodie's Abscess				
25	12	?	8/ 3/31	8/13/31	9/ 5/31	8/27/31	Closed.....	6/ 2/32
26	51	?	2/ 8/34	2/17/34	4/14/34	4/ 1/34	Treatment	
27	6	10/20/33	5/ 7/34	7/ 8/34	10/ 2/34	7/ 6/34	Closed.....	1/ 5/35
28	43	?	10/12/34	1/21/35	6/10/35	10/31/34	Closed.....	8/ 7/35
29	40	1924	1/ 9/36	1/16/36	2/12/36	2/22/36	Closed.....	2/23/36

Group 1 (Subacute Osteomyelitis).—There were 17 cases in this group; in 2 of these there were bilateral lesions. Of the 19 tibias involved by osteomyelitis, 2 required amputation, and at the time of writing the remaining 17 lesions had been closed for periods varying from one month to five and one-half years. An average period of two years had elapsed since final closure. The ages of the patients varied from 5 to 16 years. The average age at onset was 11.6 years. There were 4 girls and 11 boys. Trauma was noted as an exciting cause for localization in 10 cases. Previous infection was recognized in 8 cases. Positive blood culture was obtained in 15 cases and obtained repeatedly in 5. The organism recovered from the bone and from the blood stream was

Staphylococcus aureus in every case. In 6 cases the entire shaft was involved, with complete sequestration in 2 (cases 4 and 10). In 9 instances the lower third and in 4 the upper third of the tibia was affected. Skin grafts were used in 5 cases to hasten final closure.

Untoward Results: Ankylosis occurred in the ankle in 4 cases and in the knee in 1. In all the cases there was primary involvement of the joint, so that such an end result was anticipated. The patient in case 3, who had involvement of the knee, was discharged to a convalescent home without medical supervision, and the knee became ankylosed in about 40 degrees' flexion. An operation for the correction of this deformity is contemplated at an early date, since at the time of writing closure had persisted for over five years.

TABLE 2.—*Classification of Results According to Type of Lesion*

Type of Lesion	No.	Closed	Under Treatment	Limb Amputated	Lost	% Closed	Period from Onset to Institution of Maggot Treatment	Period of Maggot Treatment	Period from Treatment to Closure	Total Period of Illness	Time in Hospital	Time Since Closure
Subacute osteomyelitis	19	17	0	2	0	89	106 days	106 days	205 days	417 days	169 days	2 years
Chronic osteomyelitis	7	5	0	0	2*	100	23 years	48 days	393 days	24† years	132 days	2.07 years
Abscess of bone	5	4	1*	0	0	100	5 years	66 days	79 days	?	80 days	2.87 years
Average						92						

* Omitted in calculating average figures.
† Time from premaggot operation to closure.

Amputations: The cases in which amputation was performed are worthy of special consideration. The patient in case 5 was treated at another hospital, so that daily care under my supervision was impossible. The entire shaft of the tibia was involved. So many abscesses developed in the soft parts that after a few weeks almost one third of the leg was destroyed. Because of the difficulty of treating a patient in another hospital, maggot treatment was abandoned after thirty-two days. The leg was amputated about four months later.

The patient in case 6 was a boy with a history of polycythaemia vera of three years' duration. The osseous lesion involved the upper third of the tibia. Operation was done on June 3, 1932. Treatment was begun on June 12 and was continued until September 21. During this period the wound showed moderate improvement. On June 16 acute phlebitis of the popliteal vein developed. On August 18 an abscess of the posterior wall of the chest was found, which subsequently proved to be secondary to osteomyelitis of the seventh rib. Because of the poor general condition of the patient amputation at the level of the midthigh

was performed on September 27. Reamputation was necessary on December 15, and the patient was discharged from the hospital five months later.

Group 2 (Chronic Osteomyelitis).—In the 7 cases in this group there was a history of osteomyelitis of from twelve to forty-two years' duration. Four of the patients had shown closure of the lesion for long periods but entered the hospital because of local recurrences; the lesions of the other 3 had never closed. Table 2 shows that actual treatment with maggots was of fairly short duration (an average of forty-eight days). The length of the average interval, three hundred and ninety-three days, between the discontinuance of maggot therapy and final closure of the lesion was caused by a delay which occurred in a single case (case 18). The patient in this case left my care after one year and was reoperated on by another surgeon. There was no improvement, and the patient returned in about a year for further treatment. The wound finally closed after a total of four years' treatment. The average length of time from the discontinuance of treatment with maggots to closure of the lesions for the other patients in this group was one hundred and forty-six days. The period of hospitalization given refers only to the stay during which maggots were used. At the time of writing closure had persisted for an average period of two and seven hundredths years.

Lost Patients: Both the patients recorded as lost had closed lesions, but credit cannot be taken for the cures, as is indicated by the following protocols:

The patient in case 21 was transferred to a hospital for chronic diseases at a time when the leg seemed to be healing satisfactorily. During hospitalization a resection of the middle two thirds of the tibia was performed. At the time of writing a roentgenogram showed fusion of the upper and the lower end of the tibia with the fibula, which had greatly hypertrophied. The residual bone appeared fairly normal, and the wound was closed.

The other patient (case 20) fell into other hands and was operated on twice after maggot treatment was stopped. He left the hospital before closure was attained. He returned a year later. He was reoperated on, and skin was grafted into the lesion. Complete closure resulted.

Group 3 (Abscess of Bone [Brodie]).—The exact time of onset of the condition could not be determined in all cases of this group. In 2 (cases 27 and 29) it was known because of the occurrence of multiple foci; in the other 3 the lesions were "silent" at the onset. At the time of writing 1 patient was still under treatment; the other 4 had had closed lesions for an average period of two and nine-tenths years.

The patient still under treatment (case 26) had alopecia totalis and myxedema. In 1935 she had eczema around the wound and in other portions of the body. Treatment was greatly interfered with by these

complications. An operation performed on Sept. 13, 1937, revealed marked overgrowth of subperiosteal bone, with bare, eburnated necrotic bone in the depths of the wound. This was removed, and maggot treatment was begun on October 1. The lesion closed on October 23.

The entire series, then, comprises 29 cases, with involvement of 31 tibias. Two lesions necessitated amputation; the further course of 2 is not known; 1 (not included in averages) was under treatment when this report was made, and the remaining 26 lesions were closed. Exclusion of the lesions lost from observation and those under treatment leaves 92 per cent closed. The lesions in the 2 cases recorded as lost were also closed, but closure was preceded by additional operations. Closure had persisted for an average period of more than two years.

Osseous lesions have not recurred in any of the patients, although several have had severe blows over the site of the former lesion, causing abrasions of the scar. Such lesions in scars have always responded to conservative measures and have never required operation.

Roentgen Findings.—Final roentgenograms were obtained during May and June 1937. These were examined by a roentgenologist, who concluded that all except one indicated healed lesions. The exception (in case 28) showed two discrete abscesses of the upper end of the tibia, and at operation only one of these had been opened. The patient was told of the lesions but preferred to continue working until they caused trouble. The roentgenographic appearance of the bones in the other cases varied from almost perfect anatomic restoration of the trabecular architecture to extensive enlargement of the shafts, caused by overgrowth of involucrum.

COMMENT

The crux of the treatment of hematogenous osteomyelitis lies in the question of whether the lesion is actually healed or is merely covered with integument under which infection is smouldering. In this communication considerable stress has been placed on the end results, because no publications have shown the results of similar treatment. It has become customary in the literature to refer to the status of lesions as healed, improved or unimproved. I have tried to use the less misleading terms "closed" and "under treatment." The word "healed" is meaningless unless the patient has been followed for thirty or forty years. The term "improved" is equally inappropriate since, as Lewis [11] pointed out, "improvement usually means a discharging sinus or unhealed wound and indicates that surgery has not attained its aim."

The end results given by various authors in cases of osteomyelitis of all bones were summarized by Wilensky [12] in tabular form. The

11. Lewis, D.: Acute Osteomyelitis, J. A. M. A. **92**:783-786 (March 9) 1929.

12. Wilensky, A. O.: Osteomyelitis, New York, The Macmillan Company, 1934.

figures showed wide variation in the percentage of cases in which cure was recorded. Investigation of the original articles showed that the reported results were based largely on the status of the lesion at the time of the patient's discharge from the hospital, which, as Farr [13] remarked, depends on the degree of optimism of the house surgeon. My experience has been that many promising-looking lesions regress and persist for long periods after the patient leaves the hospital and that a consistent policy of after-care is necessary for really good results.

The great advantage in the use of maggots seems to lie in the high percentage of closed lesions and in the relative scarcity of recurrences. This is doubtless due to the ability of the larvae to uncover hidden sequestrums and to seek out small abscesses which might otherwise become included in the new bone. This characteristic of maggots assumes more importance since the recent demonstration by Buchman [14] that treatment with staphylococcus antitoxin and toxoid does not prevent recurrences or materially influence the progress of the local lesion. My own experience in this field, although not as extensive as that of Buchman,[14] tends to confirm his conclusions in every respect. The other advantages of treatment with maggots have been discussed fully.[15]

In criticism of maggot therapy it has been argued that the method is time consuming, expensive and painful. As shown in table 2, actual treatment with maggots occupies only 25 per cent of the entire period of disability in cases in which the condition is subacute, and in those in which it is chronic, a mere fraction of this total. The expense is not great when one considers the amount of time which is ultimately saved. A certain number of patients complain of pain, but with the use of sedatives, anesthetic ointments and frequent dressings this is never a serious drawback. Patients with long-standing wounds are willing to submit to discomfort if they can be given hope of ultimate cures.

I do not think that maggot therapy is indicated in all cases of osteomyelitis. The treatment described and practiced by Orr [8] should certainly be the ideal procedure in every case in which the condition is subacute. Only when the patient fails to make reasonable progress clinically is it necessary to consider the use of maggots. For chronic

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13. Farr, C. E.: Acute Osteomyelitis in Children, Ann. Surg. **83**:686-692 (May) 1926.

14. Buchman, J.: The Use of Staphylococcus Toxoid in the Treatment of Chronic Osteomyelitis, J. A. M. A. **108**:1151-1156 (April 3) 1937.

15. Baer, W. S.: The Treatment of Chronic Osteomyelitis with the Maggot (Larva of the Blowfly), J. Bone & Joint Surg. **13**:438-475 (July) 1931. Robinson, W., and Norwood, V. H.: The Role of Surgical Maggots in the Disinfection of Osteomyelitis and Other Infected Wounds, ibid. **15**:409-412 (April) 1933. Buchman, J., and Blair, J. E.: Maggots and Their Use in the Treatment of Chronic Osteomyelitis, Surg., Gynec. & Obst. **55**:177-190 (Aug.) 1932. Maddock and Jensen.[10]

osteomyelitis their usefulness is probably much greater. It is doubtful that anything but maggot therapy could have produced closure of some of the chronic lesions in this series. Brodie's abscess was treated with maggots because in my cases it had been opened and packed by other surgeons. This lesion is more properly managed by conservative methods, such as primary closure [16] and irrigation for a short period, with secondary closure.[17]

It is natural to wonder whether maggot therapy for osteomyelitis is a medical fad or a significant contribution to science. After seven years of experience and many trials of various substitutes I still feel that the condition can be treated profitably with maggots and that no lesion should be given up as hopeless until maggot therapy has been tried.

SUMMARY

A series of 31 lesions in 29 cases of hematogenous osteomyelitis of the tibia treated with maggots is presented. The patients were followed up to the time of writing. Twenty-six of the lesions were closed, 1 still required treatment, 2 had necessitated amputation and 2 were lost. The management of wounds under maggot treatment is described. The chief objections to treatment with maggots are the time consumed, the expense and the pain. It is pointed out that none of these objections is particularly serious. The advantages of maggots are: rapid débridement of necrotic material, discovery of hidden sequestrums and pockets of pus, stimulation of granulations, continuous treatment, shortening of hospitalization and early rehabilitation of the patient. Subacute osteomyelitis of the tibia should rarely become chronic, because of the easy accessibility of this bone.

16. Brickner, W. M.: The Treatment of Chronic Bone Abscesses by Simple Evacuation Through a Small Drill Hole, J. Bone & Joint Surg. **5**:492-500 (July) 1923.

17. Wilensky,[12] p. 231.

END RESULTS OF TUBERCULOUS CYSTITIS

REPORT OF CASES

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The problem of renal tuberculosis has received exhaustive attention for many years. It is now generally recognized that the condition is a local manifestation of a general disease, and treatment is executed with that fact in mind. Most clinical discussions begin with mention of frequency of urination as the most common chief complaint and end by saying that the vesical lesions usually heal in from six months to a year after removal of the offending kidney. However, the failure of the urinary bladder to resume a normal condition after removal of all tuberculous foci in the urinary tract is not uncommon. French writers have called attention to the necessary activity of the bladder as a possible reason for failure of the lesions to heal. For other parts of the body rest is the best method of treatment, but for the bladder rest is impossible. The change in the vesical wall may be multiple ulcers causing a painful frequency of urination or the condition may progress to produce the well known contracted and sclerotic bladder wall with an extreme reduction in capacity. The endless methods of treatment directed at the relief of this distressing condition by their very number attest to frequent failure.

With tuberculous cystitis, as with other conditions involving destruction of the normal function of the bladder, the upper portion of the urinary tract is endangered. The process may so involve the intramural portion of the ureter from the single kidney as to result in hydronephrosis and eventual destruction of the kidney. Before this occurs the capacity of the bladder may be so reduced as to cause a frequency of urination not dissimilar to incontinence. The urgent necessity of relief for both of these conditions is apparent.

Nephrostomy, cystostomy, ureterostomy and ureteral transplantation to the rectum have all been used as palliative procedures. Hinman [1] reported 4 cases in which he made ureteral transplants to the rectum because of extreme frequency of urination or a beginning dilatation in the remaining, nontuberculous kidney. In 2 of his cases he did pre-

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1. Hinman, F.: Surgical Treatment of Lower Tract Tuberculosis, Genital and Vesical, J. Urol. **20**:521-538, 1928.

liminary nephrostomies. At the time of his report (1928) 1 patient was still living two years after the operation. Hinman's paper recorded the most extensive experience I was able to find in the literature dealing with the complete destruction of function by persisting tuberculous cystitis.

As an example of the possibly destructive nature of tuberculous cystitis I wish to report 2 cases, in which there were different lesions and different operations.

REPORT OF CASES

CASE 1.—W. G. H., a man aged 22, was admitted to the hospital on May 7, 1936, complaining of frequency of urination which began in 1931. Since that time

Fig. 1.—Dilated pelvis and ureter.

the condition had become progressively worse until the time of his admission, when he was urinating every hour day and night. In January 1936 he was forced to wear a urinal. He had noticed hematuria and pyuria on many occasions.

Physical examination showed a young man in a fair state of nutrition. His weight was 128 pounds (58.1 Kg.). The lungs were clear, and the heart was normal. The right kidney was palpable and tender. The prostate was somewhat enlarged, nodular and tender. The external genitalia were normal.

The urine contained much pus and many red blood cells. Studies of the blood showed normal conditions. The nonprotein nitrogen content was 31, and the excretion of phenolsulfonphthalein was 50 per cent in two hours. A roentgenogram of the chest showed no active disease.

Cystoscopic examination with the patient under spinal anesthesia revealed a contracted bladder with much edema and many tuberculous ulcers, most marked around the right orifice. Excretory urograms demonstrated satisfactory filling in the left kidney in seven minutes (fig. 1). The pelvis, calices and ureter were

dilated to three times the normal size, and the ureteral dilatation extended down to the bladder wall. No dye appeared in the right kidney in any of the plates. Staining of urine from the bladder showed tubercle bacilli. Because of the apparently functionless kidney on the right and the dilatation of the left ureter, a nephrostomy was done on the left side on May 21. Two months later a nephrectomy was performed on the right side. The kidney showed tuberculous pyonephrosis. Guinea pigs inoculated on two occasions with urine from the left kidney showed no evidence of tuberculosis. Figure 2 shows an excretory urogram taken on July 9. Both the pelvis and the ureter were well filled and showed that improvement had taken place since the introduction of the nephrostomy tube. The patient emptied his bladder only once a day.

In April 1937, one year after the nephrostomy, the patient returned for a check-up. A pyeloureterogram (left side) taken after injection of the nephrostomy tube showed the pelvis and calices to be fairly normal, but the ureter remained dilated and tortuous (fig. 3).

Not only has this patient been made much more comfortable than he has been in several years, but a destructive process in the left kidney has been arrested.

CASE 2.—W. G. H., a man aged 54, was first admitted to the hospital on Dec. 6, 1931. The chief complaint was of dysuria and of frequency of urination, with voiding every ten minutes day and night. He had had the right kidney removed in 1914 because of tuberculosis. At the time of this operation he was having frequency of urination and dysuria. The nephrectomy wound drained for three years before healing. After this operation epididymitis developed, with draining sinuses in the scrotum.

Physical examination showed a well developed, well nourished man weighing 162 pounds (73.5 Kg.). The lungs were clear. The nephrectomy scar on the right side was well healed. A bilateral inguinal hernia was present. The epididymes were indurated, and the scrotum showed healed scars marking the site of the draining sinuses.

The urine contained many white blood cells and red blood cells. Twenty-four hour specimens of urine showed no tubercle bacilli. Cystoscopic examination showed a definitely contracted bladder. The left ureter could not be catheterized. The capacity of the bladder was 30 cc. (under spinal anesthesia). Excretory urograms demonstrated satisfactory filling of the left renal pelvis in five minutes. The pelvis and calices were apparently normal, and nothing was suggestive of tuberculosis (fig. 4). Irrigations with phenol were done. This produced some improvement in the cystitis, but the bladder could not be distended sufficiently for catheterization of the left ureter. Owing to the contraction of the bladder, which made this organ absolutely useless, the left ureter was transplanted into the sigmoid on April 14. The postoperative course was satisfactory. At the time of his discharge the patient was able to hold the urine in the bowel for three to six hours.

Excretory urograms taken as a check-up showed a normal left kidney (fig. 5A). Excretory urograms taken three years later, in 1935 (fig. 5B), showed the upper and lower calices to be dilated to twice the normal size. The middle calyx was normal. The ureter was dilated to twice the normal size. The patient returned to this hospital on Sept. 18, 1937, five and a half years after the operation, for a check-up. Figure 5C is the excretory urogram taken at this time. He was in excellent general physical condition. He stated that he was emptying his bowels about every four hours. His weight was 185 pounds (83.9 Kg.).

Fig. 2.—Excretory urogram showing reduction in the size of the pelvis after a nephrostomy.

Fig. 3.—Pyeloureterogram taken after injection of the nephrostomy tube. The size of the pelvis is approximately normal. The ureter remains dilated.

Fig. 4.—Excretory urogram taken before a ureteral transplantation.

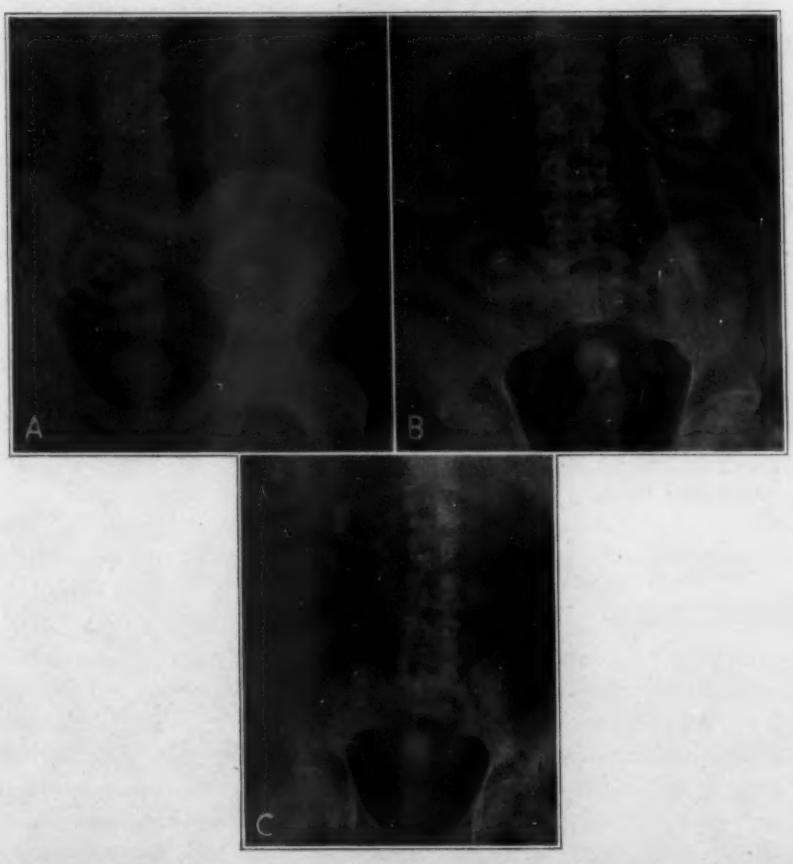

Fig. 5.—Results of ureteral transplantation: *A*, excretory urogram taken two months after transplantation; *B*, excretory urogram taken three years after transplantation; *C*, excretory urogram taken five and one-half years after transplantation.

This patient's bladder was so destroyed by fibrous tissue that instead of being an organ of convenience it had become a source of constant pain and discomfort, resulting in incontinence. Even though his remaining kidney was normal, his life was unbearable. What eventually would have happened to this kidney it is impossible to say, but the irreparable damage to the bladder made some procedure necessary.

COMMENT

These 2 cases demonstrate what occasionally may occur as the end result of tuberculous cystitis, namely: (1) destruction of an uninfected kidney by ureteral obstruction and (2) total loss of vesical function as a result of sclerosis and of destruction by fibrous tissue.

CYSTS OF EXTERNAL SEMILUNAR CARTILAGE

REPORT OF THREE CASES

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NEW YORK

Although the literature contains records of a fairly large number of cysts of the semilunar cartilages, Bennett and Shaw having recently collected 163 cases, only a few surgeons have treated the condition in more than 1 or 2 cases. I reported a cyst of the external meniscus in 1927 and did not see another until 1937. Compared with other derangements of the knee, such as torn and displaced semilunar cartilages, cysts of either cartilage are rare. Nor is it likely that many are missed or undiagnosed, because the symptoms are noticeable, and the lesion sooner or later reaches conspicuous proportions and interferes with function of the knee joint.

The symptoms of a cyst of the external semilunar cartilage are swelling, pain and variable disability. Tumefaction is the most important symptom. In the early stage the swelling is small and may be indistinguishable from the adjacent soft tissues. By the time a physician is consulted, however, the mass is visible and palpable. It is located in the interval between the tibia and the femur, at the joint line between the lateral ligament and the infrapatellar fat pad, but is distinct from both. The mass varies in size from that of a small hazelnut to that of a pigeon's egg. It is elastic, sometimes fluctuant and usually slightly sensitive to pressure. On complete extension of the knee the swelling diminishes or may even disappear by recession into the joint space, while on flexion it becomes prominent. The mass is firmly attached to the deep tissues but not to the overlying skin and subcutaneous tissues. Though there is some local sensitiveness, there is no evidence of inflammation. The swelling is readily palpated, but its limits are not sharply defined.

The pain is mild to moderate and is referred to the region of the tumefaction. It may radiate up the thigh or down the leg. Exercise increases the pain, and rest relieves it. With the majority of patients the onset of pain is insidious and seemingly is not initiated by any definite cause, such as trauma or excessive use. In a minority of cases the symptoms appear after an injury. The pain sometimes comes in attacks, being completely absent in the intervals. Finally, however, it becomes constant and fairly severe. In the early stages, when the mass is small, it does not cause any pressure on the surrounding tissues

nor does it interfere with the free mobility of the tibia on the femur; hence it does not cause discomfort. As the mass enlarges, however, it encroaches and presses on the joint capsule and the cartilage, causing pain.

The degree of disablement is variable. Most patients are able to walk as much as they please, noticing difficulty only when they first arise from the sitting position or when they first begin to walk. During attacks of moderate pain the patient may limit his activity, but he is never compelled to stop work. For sensitive persons the presence of a mass in the knee and the moderate discomfort create a physical and especially a psychic hazard which reduces activity. In an occasional case the cystic mass, which is perhaps loosely attached to the capsule, moves in and out of the joint, and the patient is aware of it; there may even be mild temporary locking of the knee. Actually, flexion and extension of the knee, both active and passive, are free. As time passes, the swelling, pain and disablement increase. The patient tires easily and may notice a continuous ache in the knee. At this stage he seeks medical aid and usually submits to an operation. I have had no experience with a patient who had harbored a meniscal cyst for many years. As this lesion occurs in young adults, who are not as hesitant about being operated on as older persons often are, and as the surgeon can assure complete relief on removal of the cyst and cartilage, one may reasonably assume that the lesion is always subjected to surgical treatment.

ETIOLOGY

Bennett and Shaw stated that the average age of the patients in 73 cases of cyst of the semilunar cartilage was 29.6 years. In my group of 4 cases, 3 presented in this communication and 1 previously reported, the average age was 28 years. Males are more frequently affected than females. These facts have led some surgeons to believe that this lesion is of traumatic origin. It is also true that there is a history of injury, sometimes rather vague, in about half the cases. Theoretically it is certainly conceivable that an injury to the front of the cartilage, damaging also the capsule, might result in a hematoma which might undergo cystic degeneration. The cyst or cysts, being loosely encapsulated, become enlarged, interfere with the local circulation and cause further cystic degeneration. A vicious circle is established, and the result is a cystic mass of the meniscocapsular tissues. Yet it is difficult to set aside the fact that there are no cysts in the hundreds of injured and dislocated meniscuses which physicians see and remove. Dr. H. L. Jaffe, pathologist at the Hospital for Joint Diseases, in discussing this problem with me, stated that he has at times seen microscopic cysts in the torn cartilages which I have sent to his laboratory. Clinically, however, I surely do not see any gross

multilocular encapsulated cysts in the removed meniscuses ruptured and dislocated by injury. It is worth recalling too that while the internal meniscus is damaged nine times more frequently than is the external meniscus, cysts occur much more often in the latter than in the former. It has been suggested that an injury may cause pinching off of a bit of synovial tissue, which, becoming encapsulated, gradually forms a cystic mass. This theory seems plausible because the cells lining the cysts and those lining the synovial tissue are histologically analogous. The specificity of the lesion and its location lead me to believe that it is caused by a metabolic disturbance in the cartilage, initiated by trauma or some unknown factor, as a result of which the cartilage cells necrose. Thus are formed defects which coalesce into cysts.

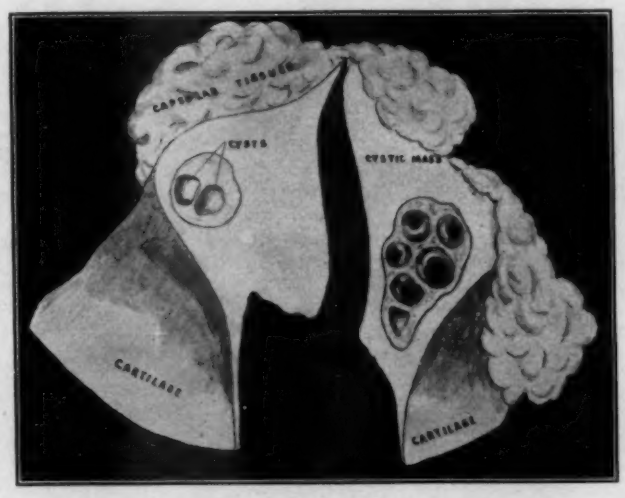

Fig. 1 (case 1).—Schematic drawing of the sectioned specimen. Multiple cysts of unequal size, encapsulated in the meniscocapsular tissues.

PATHOLOGIC PICTURE

The lesion under consideration consists of a multilocular cystic mass situated at the anterior border of the anterior or middle third of either the external or the internal meniscus. Parenthetically, it should be noted as a point against the theory of a simple traumatic cause that although the posterior third of the meniscus is often injured a cyst is never seen in that segment of the cartilage. The cystic mass (fig. 1) is enclosed in loose connective tissue and lies in the meniscocapsular tissues. The cystic mass is actually in and part of the peripheral portion of the cartilage. This location at and in the meniscocapsular junction makes it difficult to determine whether the cysts arise primarily in the cartilage and extend into the fibrous capsule, or whether

they form first in the capsulosynovial tissue and secondarily invade the cartilage. There are usually many cysts, some small, others large, filled with mucinous, glairy material. There is a limiting membrane, but this is loose, vascular and poorly defined.

The microscopic section shows a multilocular cystic area lying between and united to the cartilage and the capsule. A cross section (fig. 2) may conveniently be divided into an avascular segment (*A*),

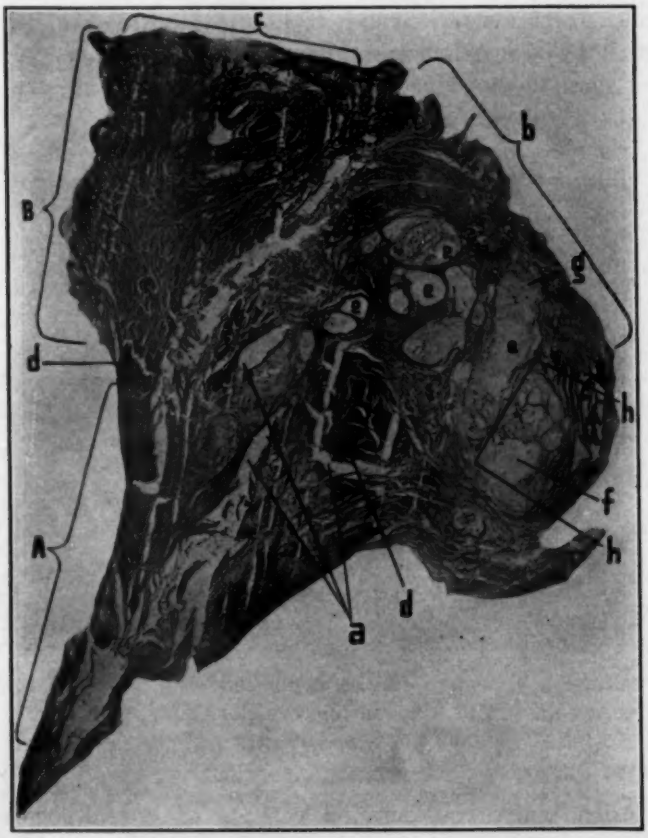

Fig. 2 (case 1).—Cross section of the cartilage and cyst, × 5. *A*, avascular portion, containing cartilage with (*a*) areas of degeneration in it. *B*, vascular portion, including the periphery of the cartilage (*d*), the cystic mass (*b*) and the capsulosynovial tissue (*c*). The cysts (*e*) are of different size; some of them have distinct walls (*e'*) while others are enlarging and coalescing, having no limiting membrane or a poorly defined one (*g*).

containing the cartilage, in which are to be found small areas of degeneration (*a*), and the vascular portion (*B*), in which are included the cystic mass (*b*), the capsule and synovial lining (*c*) and the periphery

of the cartilage (*d*). The cysts in places have well defined walls of connective tissue lined with flat cells (*e*). In other sections one notes connective tissue cells in the process of degeneration (*f*). The cysts are filled with mucinous material. The origin of this is uncertain. It may be the result of secretion of the lining cells, or it may arise from the liquefaction of the connective tissue and lining cells, that is, it may

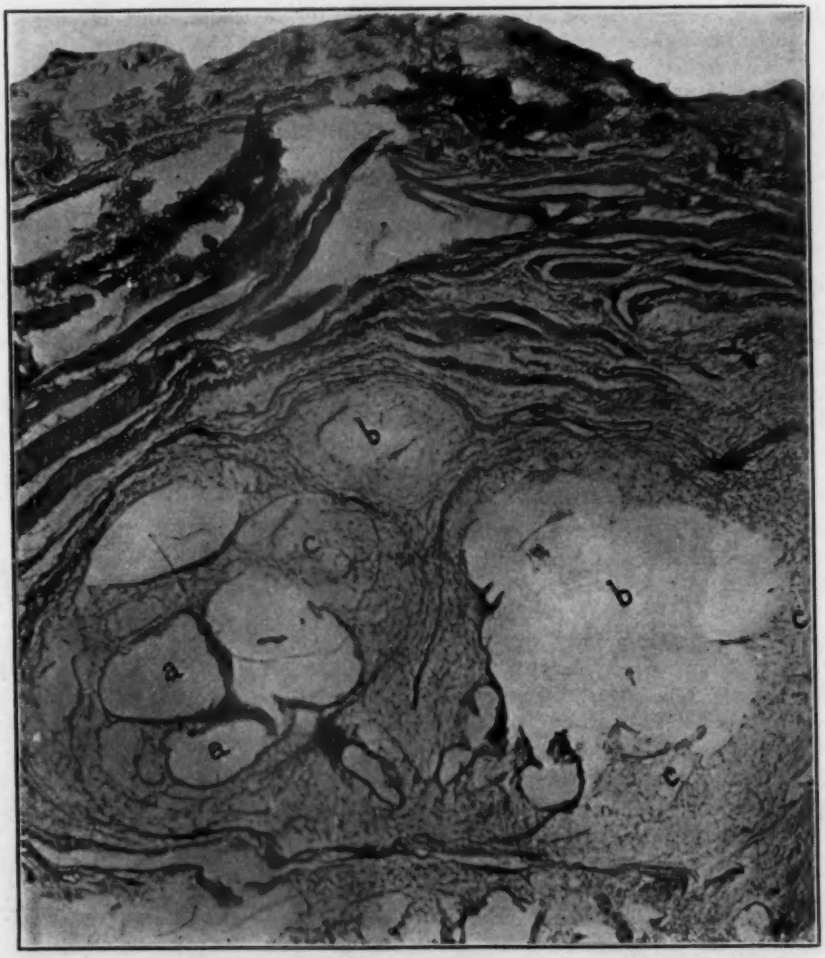

Fig. 3 (case 1).—Enlargement (× 30) of the section marked *hh'* in figure 2: *a*, cysts with lining membrane; *b*, cysts without distinct lining cells, in the process of formation and enlargement; *c*, degenerating connective tissue cells.

be a product of degeneration. The cells of the lining membrane of the cysts are histologically analogous to those of the synovial tissue; this fact suggests the possibility of traumatic isolation and enclosure of some of the synovial tissue, which in its growth may form cysts and encroach on the cartilage.

REPORT OF CASES

CASE 1.—N. K., a man aged 27, was referred to me in September 1936. His chief complaint was of pain and swelling on the outer side of the right knee. The symptoms had first appeared about two years previously, following a fast game of handball. He began to have pains in the lateral aspect of the right knee joint. Several weeks later a swelling appeared in this region. The pain was increased by weight bearing and relieved by rest. At times the knee gave way suddenly, as a result of which the patient had cultivated the habit of rising from the sitting position with the knee completely extended, thus avoiding the likelihood of falling. He had never had any locking of the knee.

Examination showed a swelling on the outer side of the right knee, in the region of the external semilunar cartilage. The swelling was about 2 inches (5 cm.) in diameter and was moderately sensitive to pressure. On extension the mass almost completely disappeared, while on flexion it became conspicuous. Palpation revealed that the mass was intimately bound down to the deep tissues. A roentgen study of the knee gave negative results. A diagnosis of cyst of the external semilunar cartilage was made.

The patient was admitted to the Hospital for Joint Diseases, and operation was performed on October 12. A vertical incision 5 inches (12.5 cm.) in length was made over the outer aspect of the knee. The deep tissues were incised vertically, and a mass about the size of a pigeon's egg was seen at the joint line, in intimate association with the external semilunar cartilage. The cartilage and cyst were removed in one mass. The specimen showed that the cyst was part of the semilunar cartilage (figs. 1 and 2). The cut section of the gross specimen (fig. 1) showed a multilocular cystic mass. The report of the pathologist, Dr. Henry L. Jaffe, was as follows: "Gross examination: The specimen consists of an external semilunar cartilage considerably enlarged in its central portion, owing to cystic transformation of the parameniscal tissue [fig. 2]. Microscopic examination: The section shows a meniscus with parameniscal multilocular cysts. The meniscus itself shows considerable degeneration, with small cystic spaces [*a* in fig. 2*A*] developing within its substance."

In this instance it may very well be that there was a primary degenerative process within the periphery of the cartilage, resulting from the degeneration of the cartilage cells. The cyst enlarged and advanced, causing further degeneration of the cartilage and involvement of the capsular tissue. The actual pathogenesis is nevertheless a matter of speculation.

This patient had an uneventful convalescence. The wound healed by primary union. At the time of writing the knee is stable and freely movable. The patient was reexamined on Dec. 15, 1937 and was found to be entirely cured.

CASE 2.—L. H. R., a man aged 34, was referred to me in June 1936. His chief complaint was of pain of about six months' duration on the outer side of the right knee. There was no known antecedent injury or illness. The pain, which appeared only when the patient was walking, was mild, and it disappeared in a week. It recurred periodically and with increasing severity. It was localized on the lateral side of the knee. There had been no "locking" and no effusion into the knee, but there was a clicking sensation when the knee was bent. Occasionally the knee "gave way" as if it had been kicked from under him, and he fell. There had been no limp, and the patient could walk as much as he pleased.

Examination showed an easily palpable, apparently fluctuating mass as large as a pigeon's egg on the outer side of the right knee, in the vicinity of the external semilunar cartilage. There was no local tenderness, and no evidence of inflammation was present. The mass was firmly attached to the deep tissues.

The skin and subcutaneous tissues were freely movable. A roentgen study of the knee revealed no pathologic change in the bone. A diagnosis of cyst of the external semilunar cartilage was made, and operation was performed on June 12. A short vertical incision was made over the anteroexternal aspect of the right knee, the middle of the incision being over the joint line. The incision was extended through the aponeurotic expansion of the vastus externus muscle. When the edges of this aponeurosis were retracted a mass about the size of a large marble was exposed. This was beneath and intimately bound down to the capsule of the joint. The joint capsule was incised transversely above and below the mass to permit removal of the cartilage and cyst en masse. The wound was closed in layers. An incision was made through the mass and the meniscus. The

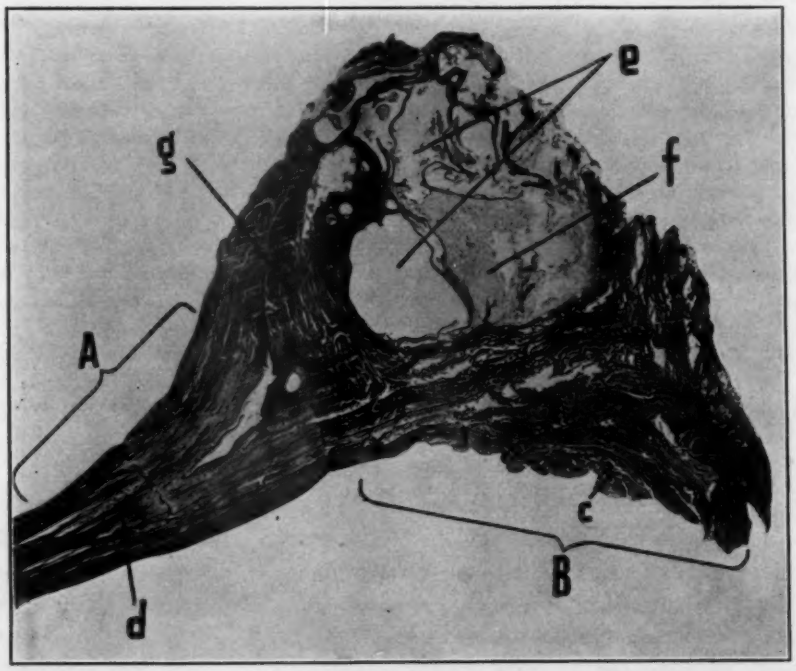

Fig. 4 (case 2).—Cross section (× 5) through the largest diameter of the specimen: *A*, avascular portion of the meniscus; *B*, vascular portion containing the periphery of the meniscus, the cyst and the capsule; *c*, synovial membrane; *d*, areas of degeneration in the cartilage; *e*, cysts; *f*, mucinous material in the cyst; *g*, periphery of the cartilage.

mass was a multilocular cyst (fig. 4) containing glairy mucoid material. It was thoroughly embedded in the periphery of the fibrocartilage and was intimately attached to the capsule of the joint. Dr. Henry L. Jaffe reported on this specimen as follows: "Gross examination: The specimen consists of a somewhat enlarged meniscus. In the parameniscal tissue there is a multilocular, thin-walled cystic structure containing mucinous secretion. At one point, penetration of the cyst into the meniscus proper is observed. Microscopic examination: Sections show typical changes of parameniscal cyst formation with extension of the cyst to the meniscus proper. The meniscus itself shows degenerative changes, with tiny cystic spaces [fig. 4, *d*]. The extrameniscal cysts are in various stages of evolution. They apparently have arisen by liquefaction of degenerated and

softened connective tissue at the meniscocapsular border. These cysts are lined by flattened cells, apparently modified connective tissue cells. The tiny intrameniscal postdegenerative spaces are for the most part unlined."

This lesion was evidently the usual type of cyst of the external semilunar cartilage, beginning insidiously and progressing over a period of several months to a point at which it caused disability and sensitiveness of the knee joint. The histologic study gave no clue as to whether the cyst was first formed in the capsular tissue and then invaded the meniscus or whether it occurred immediately as a degenerative process of the meniscal tissue.

The operative result was entirely satisfactory. The wound healed per primam intentionem. The patient regained a normal range of motion and full control of the knee joint.

CASE 3.—C. B., a woman aged 19, was referred to me in January 1932 because of pain in the left knee. The pain had begun four years previously without any apparent cause. It appeared intermittently in more or less severe attacks. The attacks increased in severity, so that the patient finally sought medical aid. The pain was always increased by walking and relieved by rest. The patient stated that at times she was suddenly aware of "something slipping in the knee and getting out of place." When this occurred she flexed the knee acutely and was promptly relieved.

Examination showed that the patient walked without a limp. The left knee presented a distinct swelling on the outer aspect, in the region of the joint line, directly in front of the lateral ligament. The mass was cystic and fluctuant. It was somewhat tender to pressure. Flexion and extension of the knee were free. There was no abnormal anteroposterior, rotary or lateral motion. A diagnosis of cyst of the external semilunar cartilage was made. An operation was advised but was not performed by me. Attempts to trace this patient have been unsuccessful.

SUMMARY

Cyst of the external semilunar cartilages is a distinct entity which is easily diagnosed clinically. The lesion occurs chiefly in young adults, more frequently in males than in females. It is located in the meniscocapsular tissues. Its genesis is uncertain. As there is a history of injury in many cases, some surgeons believe that the lesion is initiated by an injury to the cartilage, as a result of which there is a hemorrhage with subsequent degeneration and liquefaction of the hematoma followed by cyst formation. Actually there are many cysts, some of which coalesce to form large cysts. Some are lined with a distinct connective tissue membrane covered with flat endothelial cells or perhaps with modified connective tissue cells resembling those which line synovial tissue. The lesion may represent a degenerative process in the meniscocapsular tissues, secondary to a vascular disturbance initiated by a trauma or other cause. Doubt as to whether trauma is an important etiologic factor arises from the fact that in the large number of cases of rupture and displacement of the semilunar cartilages caused by injury, no instance of a multilocular cyst has been observed. Fortunately the treatment is not dependent on knowledge of the cause. Removal of the cyst and the cartilage affords complete relief, and thus far no recurrence has been reported.

REVIEW OF UROLOGIC SURGERY

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(Concluded from Page 696)

PROSTATE GLAND

Physiology.—Farrell [35] described a method by which pure prostatic fluid may be obtained for study. The action of drugs on the prostate gland has been noted, as well as the response to electrical stimuli. The prostatic secretion of the dog is consistently acid. The secretion, as demonstrated by its intravenous injection or by perfusion experiments, has no great toxicity.

Many of the substances used therapeutically in urologic practice are secreted by the prostate gland. These substances do not appear to enhance the bactericidal action of the prostatic fluid. The normal prostatic fluid has a bactericidal action. The exact cause of this action is not known. Experiments are now being conducted to determine it.

Alcohol is eliminated by the prostate gland in measurable amounts. It has a deleterious action on the viability of sperm. Alcohol may be a factor in sterility.

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35. Farrell, J. I.: The Newer Physiology of the Prostate Gland, J. Urol. **39**:171-185 (Feb.) 1938.

Hypertrophy.—Mussgnug [36] stated that damaged renal function in a patient with hypertrophy of the prostate gland is not always the result of residual urine and infection but that a toxic agent is also a factor. To prove this hypothesis he injected an extract of canine hypertrophic prostate gland into one series of dogs, and into another series he injected an extract of human hypertrophic prostate gland. There were two series for controls; one series was given injections of an extract of normal canine prostate gland, and the other was given extracts from other organs (the spleen, the liver, the thyroid gland, the musculature and the testis).

Regular examinations were made of the urine, the blood pressure and the concentration of urea in the blood, and the kidneys were examined microscopically at postmortem examination. The animals used as controls failed to show damaged renal function after the injections had been continued for half a year.

The animals given injections of extract of human and canine hypertrophic prostate gland all showed decreased renal function within a few weeks, which in many instances led to death. Anatomically Mussgnug found a primary toxic injury of the glomeruli with secondary degenerative changes in the tubules. The changes were similar to the renal changes observed during pregnancy. In experiments performed with the animals under general anesthesia, when the ureter was exposed and an extract of hypertrophic prostate gland was injected intravenously, ureteral peristalsis was discontinued.

Mussgnug concluded that the best procedure is to remove the hypertrophic prostate gland at operation as radically as possible in order to make sure of removal of the toxic focus.

Young [37] stated that transurethral operations have proved satisfactory in treatment of obstructive conditions at the vesical neck, particularly contractures, bars and moderate enlargements. When the disease has progressed much beyond this stage, according to statistics of a number of operators, enucleation of the prostate gland (preferably through the perineum) is the method of choice. By this means it is possible to see and feel the prostate gland, which is brought down by the tractor so that it may be examined carefully. A portion may even be excised for microscopic study if necessary. Thus the presence of early malignant changes may be detected and radical operation carried out. If the process is not malignant (in about 1 in 5 cases it is malignant) enucleation of the hypertrophied lobes from within the prostate gland may be carried out cleanly, the hemorrhage being completely

36. Mussgnug, H.: Ueber die Entstehung der Nierenerkrankung bei Prostatahypertrophie, Ztschr. f. urol. Chir. u. Gynäk. **43**:497-526 (Jan.) 1938.

37. Young, H. H.: Some Problems in Surgical Treatment of the Prostate, J. A. M. A. **110**:280-283 (Jan. 22) 1938.

arrested by ligatures and sutures and the operative wound closed. This method provides a clean surgical technic, and one has the satisfaction of preventing sloughing and infection, which frequently persist for a considerable period after transurethral operations and lead to painful prostatitis in the remaining glandular tissue, to cystitis and to irritation; the symptoms of these conditions are frequently worse than those associated with obstruction.

Tillisch [38] reported a case of hyperplasia of the prostate gland. The patient, a man aged 29, came to the Mayo Clinic because of difficulty of urination. His present trouble had started several years before he was seen at the clinic and consisted of hesitancy in starting urination and scantiness of the urinary stream. There had been gradual increase in the severity of symptoms until one year previously, when severe frequency and urgency of urination had developed. A roentgenogram of the kidneys, ureters and bladder, taken elsewhere at that time, had revealed vesical calculi, which were removed cystoscopically. After this procedure the patient had complete relief of pain but frequency of urination continued, and he had nocturia (two to three times each night). There also was an increase in hesitancy; the stream became smaller, and the patient had the sensation of incomplete emptying of the bladder.

Examination of the prostate gland by rectum revealed a boggy gland, apparently normal in size. Results of urinalysis were negative. Cystoscopic examination revealed definite hypertrophy of the lateral lobe of the prostate gland, projecting anteriorly, and definite commissural enlargement. Transurethral resection was performed, and 4 Gm. of tissue was removed.

Thompson, in a discussion of the case, pointed out that an unusual feature is the fact that the obstructing tissue removed from the prostate gland, although the patient was only 29 years old, was similar to the adenofibromatous hyperplastic tissue which frequently causes obstruction of the prostatic urethra in elderly men. Tillisch's patient was the youngest patient with such a lesion to be seen at the clinic.

The cause of this patient's difficulty in urination was easily recognized through use of a cystoscope equipped with a system of retrograde lenses. The nodular appearance of the left lateral lobe of the prostate gland, which projected anteriorly, was grossly typical of adenomatous hyperplasia, and microscopic study of the removed tissue verified the impression.

Obstruction at the vesical neck rarely occurs in a young man. In the majority of cases either a median bar or a contracture of the vesical neck secondary to chronic prostatitis is present.

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38. Tillisch, J. H.: Hyperplasia of the Prostate Gland: Report of an Unusual Case, Proc. Staff Meet., Mayo Clin. **13**:62-63 (Jan. 26) 1938.

Carcinoma.—Walthard [39] examined 100 prostate glands of men more than 40 years of age. The specimens were obtained at necropsy. None of the patients had died from disease of the prostate gland. The glands were cut in series, and every third section was examined. The results of this concise and thorough study are extremely interesting and influence one's views regarding prostatectomy.

In 30 cases Walthard observed an undeniable carcinoma of the prostate. In no case could the diagnosis be made before necrospy was performed, nor had the patient during his stay in the hospital shown any sign of prostatic malignant tumor. In 25 cases signs of malignant infiltration were observed; in 5 cases the typical picture of carcinoma was observed without any infiltrative growth into the regional tissue.

In the overwhelming majority of cases the carcinoma was in the prostate gland itself, that is, in the surgical capsule around the adenomatous nodules of the periurethral glands which form the surgical prostate gland. In 24 cases carcinoma occurred in its caudal part, between the colliculus seminalis and the caudal end of the gland, according to Young's findings. In 5 cases the carcinoma was situated both in the caudal third and in the middle third of the prostate gland, and in only 1 case was it near the bladder. In 4 instances carcinoma was observed in a benign nodule, but in 3 of these it could be demonstrated that the malignant growth had infiltrated the benign nodule only secondarily, from the outside.

As carcinoma and benign hypertrophy occur in patients of the same age groups, the surgeon can draw the following conclusions:

When an operation for hypertrophy of the prostate gland is necessary, there is a probability that carcinoma is concomitantly present in 30 per cent of cases. If it is desired to give prophylactic treatment for the carcinoma as well as to remove the obstacle to free outflow of urine, the perineal route should be used. From the point of view of prophylaxis, perineal prostatectomy is superior to transurethral resection or suprapubic enucleation. It is the only approach which gives a clear view of the prostate gland, allowing removal of the hypertrophied adenomatous nodules, as well as the anatomic prostate gland (the surgical capsule), extensively enough for sufficient prophylaxis. Although the mortality rate (4 per cent) of prostatic carcinoma can in no way be compared with the morbidity rate (30 per cent), one can never tell in which case the carcinoma may spread and cause clinical symptoms.

Chauvin [40] stated that no single form of treatment is applicable in all cases of cancer of the prostate. In cases in which the malignant

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39. Walthard, B.: Die Häufigkeit und Histogenese des Prostatacarcinoms, Ztschr. f. urol. Chir. u. Gynäk. **43**:483-496 (Jan.) 1938.

40. Chauvin, E.: Cancer of the Prostate, Kong. d. internat. Gesellsch. f. Urol **2**:98-102, 1937.

tumor has developed but slightly, the growth is certainly amenable to surgical removal; this can be accomplished by simple enucleation (Freyer), often with simultaneous removal of the seminal vesicles, which may have been invaded.

A tumor of moderate development offers a more difficult problem. In the presence of such a tumor the capsule is invaded or even transcended but the tumor remains well limited. Wide prostatectomy, whether transvesical (Pauchet) or perineal (Young), is too grave an operation (46 per cent mortality); in addition, it destroys the sphincters, leaving the patient incontinent, and does not remove the danger of metastatic foci causing extension, especially in the bone. Chauvin has given up such destructive operations in favor of the use of radium, which is a valuable remedy and is attended with less risk. He disposes of the objections that it is horribly painful, that it is ineffective, that it encourages metastasis and that it is useless. It is not painful, or at most it causes very little pain, if applied by the perineal route. It is ineffective only when the technic is faulty. Irradiation must be homogeneous and prolonged; all parts of the tumor must receive an equal dose, and applications must be maintained for eight or ten days. The needles must carry a charge not exceeding 2 mg. of radium element.

Chauvin has treated 56 patients by this method, with only 3 failures and 3 recurrences. As for metastasis, it, too, is caused by faulty technic, inadequate doses and uneven application. If radium is properly applied, metastasis is not more extensive after its use than after surgical extirpation and is possibly less so. Radium therapy cannot be called useless when the alternative is retention of urine, followed by the slow agony that is the lot of a patient on whom cystostomy is performed.

Although cures by radium therapy are rare, they are nevertheless possible, in so far as one may speak of a cure of cancer. Chauvin recorded his results as follows: Among 56 patients treated with radium there were only 5 deaths (8.9 per cent). Application of radium caused little discomfort when it was not made intravesically; there was none of the intense vesical tenesmus reported by certain authors. The action of the radium was surprising in its rapidity, its definiteness and, one might almost say, its constancy. After removal of the needles the lesions were found to be destroyed: there were no more nodules and no inequalities of form or consistency. The tumor was replaced by a uniform mass, dense but not hard, which formed a lining behind the symphysis. In only 4 cases did failure occur. Late results were still more interesting. Recurrences in situ are exceptional in such cases; Chauvin has had only 4. Metastasis appears to be more frequent. Its incidence cannot be determined with any exactitude, because patients with this condition come only exceptionally into the urologic service. With

radium, as with the knife, one may expect only purely local action. Chauvin has seen 2 of his patients in perfect health five and six years, respectively, after treatment.

Functional results were good in the great majority of cases. Almost normal micturition resulted in cases of chronic retention and ischuria; cystostomy was necessary in only 6 cases. These results were obtained at the expense of discomfort which is insignificant when one considers the gravity of surgical intervention and the suffering caused by it.

For a tumor of the third stage, which has cleared the capsule and has advanced to any extent into the pelvis, nothing is to be expected from the use of radium. Only palliative therapy is applicable.

Pasteau,[41] like others, made many attempts to find clinical signs that would lead to a definite early diagnosis of cancer of the prostate gland, but he failed. He stated that in his opinion the radical operation is not advisable. He stated also that treatment with roentgen rays or radium is not followed by cure but is, on the contrary, followed by intense pain and by accelerated extension of the malignant process. He has adopted the following course:

1. Because a prostate gland removed with a diagnosis of simple hypertrophy frequently contains nodules of malignant degeneration and because with such a condition suprapubic prostatectomy is followed by cure or by such long survival without pain or complications that one may speak clinically of cure, immediate and rapid prostatectomy is recommended when there is any doubt as to the nature of the lesion. The surgeon who makes it a practice to remove a prostate gland for simple hypertrophy is, in effect, controlling cancer of the prostate gland.

2. When the diagnosis of cancer is almost certain, it is better not to arouse illusory hope in the patient by surgical intervention. Radium and roentgen therapy, in view of their poor results are not recommended. The mechanical complications caused by retention should be cared for, and when retention occurs the bladder should be drained by suprapubic cystostomy. Precautions should be taken to assure subsequent cleanliness, this being the best means of preventing the severe infection which may occur when the bladder is not sufficiently emptied. Thus the fatal termination is retarded as much as possible, and the patient is saved from needless pain.

Lasio[42] stated that treatment of cancer of the prostate gland, after the illusory results given by major operative methods, has in the last decade turned to physical therapy and especially to the use of roentgen rays and radium.

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41. Pasteau, O.: Cancer of the Prostate, Kong. d. internat. Gesellsch. f. Urol. **2**:96-98, 1937.

42. Lasio, G. B.: Treatment of Cancer of the Prostate, Kong. d. internat. Gesellsch. f. Urol. **2**:124-130, 1937.

From an etiologic point of view, three main varieties of cancer of the prostate gland can be distinguished: (1) primary prostatic cancer in an organ which has not been invaded previously by any other kind of neoplasm, (2) cancer in an adenomatous prostate gland, and (3) cancer of the capsule of the prostate gland, or, more precisely, cancer developing in the fibroadenomatous glandular capsule of a prostatic adenoma that has been extirpated or that has not yet been operated on.

Lasio explained cancer as degeneration of the adenoma or as the result of irritation, degeneration and atypical proliferation of the epithelial cells of the true prostate gland. He reviewed all the symptoms in an effort to find signs that might aid in early diagnosis but concluded that this is still impossible. Such means as are available allow the discovery of the cancer only after it has reached a stage too advanced for any attempt at radical cure.

Lasio's personal observations were based on 1,855 cases of adenoma of the prostate gland, in 155 of which a beginning carcinoma was found. This material, however, did not lend itself well to the solution of problems concerning pathogenesis; it happened either that only the adenoma and not its capsule was examined microscopically, or the adenoma was found absolutely free from cancerous degeneration (the proper study of which would require the examination of serial sections throughout the entire organ, which has never been rigorously done, according to any statistics published).

It may be considered proved that from unquestionably benign hypertrophy a malignant transformation may develop, just as a cancer may start from a vesical papilloma. The secret of operative success lies in early diagnosis, while the process is limited to the prostate gland and its involucrums, with guarantee of absence of lymphatic metastasis. Clinical methods are not equal to this task. No method now exists which enables the surgeon to arrive at an early diagnosis. To this fact Lasio attributed the failures following his operations, results which, he stated, are shared by the majority of surgeons.

In cases of retention, permanent cystotomy is indicated to relieve suffering and to prevent infection; the exclusion of the cancerigenic zone arrests to some extent the development of the cancer, which is no longer subjected to irritative functional, instrumental and septic stimuli. Fifty per cent of Lasio's patients who were operated on received great benefit from this treatment, so that they gained in weight and in some cases asked for closure of the fistula, believing themselves cured.

The hypogastric route offers the advantage of permitting direct application of radium and roentgen rays, but Lasio's results were so poor that he gave up the method. Application of radium by way of the urethra gave a good local result but accomplished nothing definitive. The outcome in 2 cases in which radium was placed in the bed of the

adenectomized prostate gland was fatal within one and three months, respectively. Transvesical prostatectomy followed by radium therapy by way of the hypogastrium and the urethra was followed by death in two months; the same treatment with application of radium in the hypogastrium and the perineum prolonged life for six months. Perineotomy with infixation of needles by way of the perineal route in 3 cases was followed in 2 by death within a year and in 1 by clinical improvement but by no local effect.

Results of this kind are not encouraging, and Lasio concluded that new experiments must be tried if better results are to be obtained.

Bonanome [43] reviewed the statistics concerning 952 patients with disease of the prostate gland treated in his clinic at Rome, Italy. Eight hundred and fifty of these had prostatic hypertrophy, and 102 had cancer of the prostate gland. Of the cases in which cancer was present, the diagnosis was certain in 66; in the other 36, operative and histologic control was wanting. In terms of percentage of the whole, the cases of cancer constitute 12 per cent of the series, which decreases to 7.7 per cent if only the 66 fully proved cases are considered. These figures are not far from those of Ascoli (7.7 per cent) and of Blatt (7 per cent) but are far below those of Mingazzini (21 per cent) and of Young (18 per cent). All these figures might be increased if it were possible to compile, in addition, statistics regarding the later evolution of the cases, including the histologic reports. The difficulty of making a differential diagnosis between chronic prostatitis and cancer of the prostate gland is well known.

If it were possible to distinguish clinically between cancer derived from the submucous glands of the vesical neck and cancer derived from the true prostate gland, the first could be treated with enucleation, as in the case of ordinary prostatic hypertrophy, provided that operation was done early and metastasis had not occurred. In the treatment of cancer of the true prostate gland Bonanome has abstained from radical operation and has addressed himself to the relief of certain symptoms, such as retention, dysuria, ischuria and hematuria, by performing cystotomy or by use of transurethral electrotomy associated with roentgen therapy. Pollakiuria is greatly benefited by roentgen therapy; in some of the author's cases it disappeared in two days, with diminution or cessation of burning and pain on urination. The jet increased in force and caliber, and the general condition of the patient improved greatly. In some cases, however, benefit does not follow this treatment.

The behavior of metastatic foci in bone is interesting, such foci having been sensitive to irradiation. In 1 case, in which there was

43. Bonanome, A. L.: Treatment of Prostatic Cancer, Kong. d. internat. Gesellsch. f. Urol. **2**:132-136, 1937.

bilateral sciatica and in which roentgen examination of the spinal column and the pelvis revealed typical dissemination of osteoplastic metastases, rectal examination established the existence of a small nodule that was undoubtedly carcinomatous. Roentgen therapy addressed to the metastatic foci caused gradual disappearance of the excruciating pain to such an extent that the patient was able to give up the use of morphine. He was still free from pain when examined five years later.

The method of irradiation is that of Coutard, with prolonged sittings and large doses. Usually 5,000 to 7,000 roentgens is given, the territory being divided into five fields: two suprapubic (with crossed foci) two sacral (with similarly crossed foci) and one perineal. In each field 1,000 to 1,300 roentgens is distributed, with 200 roentgens per application. Applications are given twice a day if a reaction does not occur. A cycle of treatment lasting about two weeks is given, if well tolerated; this is repeated every six months or may be repeated in three months if indicated.

Chevassu [44] expressed the opinion that in view of the slow evolution of cancer of the prostate gland in many cases it is difficult to assert that a service has been rendered to a patient when the treatment has done nothing more than permit him to live a few years longer. Lasting cures under histologic control are altogether exceptional.

For a good many years Chevassu has not used the dangerous radical operation but has used radium therapy. He has planted needles simultaneously at the back of the prostate gland (after prerectal décollement) and at the top by way of the bladder (after a cystostomy had been performed and the wound left open). By this method he had obtained complete clinical obliteration of the cancerous indurations. He has never seen, however, a single definite cure. The patient of whose condition he was most proud suddenly succumbed to paraplegia, and roentgen examination revealed an "ivory vertebra" that was beyond doubt neoplastic.

As the result of these experiences, at present he either employs no surgical treatment or does a prophylactic cystostomy. He admitted that the inadequacy of this treatment is lamentable but stated that he knows of no better way. He stated his definite opposition to the use of partial resections, saying that if the tumor is really cancer such a procedure is likely to act as a whip to speed its progress. He spoke of true cancer of the prostate gland and did not discuss prostatic hypertrophy associated with so-called nodules of neoplastic degeneration. It is always difficult to affirm that adenomatous zones in a state of proliferation in prostatic hypertrophy, examined after extirpation, are

44. Chevassu, M.: Treatment of Cancer of the Prostate, Kong. d. internat. Gesellsch. f. Urol. **2**:114-120, 1937.

really cancer, and statistics on prostatic cancer cannot be based on observations of this kind. He expressed agreement with Oreja that all men more than 50 years of age should be examined systematically by rectum in order to assure early diagnosis.

For differential diagnosis between chronic prostatitis and cancer, retrograde urethroprostatography is today available, for in cases of prostatitis it is usual for one or more intraprostatic caverns to appear in the picture. Chevassu's experience with this method of exploration has shown him that among old men who have a hard, immovable prostate gland, cancer is the more frequent of these two conditions; chronic prostatitis, however, is not exceptional. Although this method readily permits recognition of chronic prostatitis, the images are so variable for cancer that it is often difficult to diagnose the latter with certainty. Everything depends on the relation of the cancer to the urethral canal. In cases of advanced cancer the urethra presents ulcerous and vegetating lesions with irregular outlines that do not resemble those of prostatic hypertrophy. In other cases, however, the urethra appears practically normal. Chevassu illustrated on the screen a case in which a normal urethra was projected on a skeleton of the pelvis, packed with neoplastic nodules caused by cancer (diagnosis proved at necropsy). He concluded that when a hard, nontuberculous prostate gland shows no caverns on urethrographic examination, cancer should be considered present if the induration does not yield to hot rectal lavages and to antisyphilitic treatment. He did not venture to say what form of treatment under such conditions is the wisest to carry out, even when diagnosed early.

Retrograde urethroprostatographic study with iodized poppyseed oil has never given rise to untoward symptoms in a series of 800 cases in which it has been used since 1933. Iodized poppyseed oil should never be used in a bleeding urethra, and retrograde urethroprostatographic examination should always be performed under fluoroscopic control. When employed with proper technic it is a remarkable method of examination.

Keyes [45] stated, in a discussion of papers by Hryntschak, Nitch and Oreja, that the clinical meaning of the term "early" will vary with each generation of urologists. Today one considers as an "early" cancer one which has not extended palpably beyond the prostate gland. Such a cancer may belong to any of three types.

1. Cancer arising within a hypertrophied portion of the gland; such a growth is removed entirely by prostatectomy for adenoma. Every surgeon knows by experience that sections of an ablated adenoma

45. Keyes, E. L., in discussion on Symposium on Treatment of Cancer of the Prostate, Kong. d. internat. Gesellsch. f. Urol. **2**:92-94, 1937.

may reveal a small central carcinoma the existence of which had not been suspected. One expects that a patient after such ablation will not show further evidence of cancer.

2. Cancer which can be felt by rectum as an irregularity on the posterior surface of the gland. Such an irregularity, however, may be suggestive of chronic prostatitis rather than of carcinoma.

3. Cancer plainly palpable as such by rectal palpation against a sound in the urethra. In a large proportion of cases of such involvement metastasis has already occurred.

It will doubtless be necessary in the future to restrict the term "early" to the first two classes of cancer: (1) cancer discovered by the pathologist (postprostatectomy), and (2) cancer not to be distinguished as cancer by rectal palpation, even if this is made against a sound in the urethra.

Keyes stated that his first implantation of radon was performed in May 1931. His third patient, operated on in October 1931, was alive and seemingly well at the time of writing. There were no five year cures. Of his 14 patients operated on more than three years prior to his report, 4 were alive and well, and these 4 were the only ones among the 14 whose condition was diagnosed at biopsy while rectal palpation still gave a doubtful impression.

In the last three years, 27 patients with cancer have been operated on by various surgeons, with 1 postoperative death. The condition in 10 cases was diagnosed by aspiration biopsy while still not positively diagnosed by rectal palpation. Four of the patients died; 1 had a recurrence after twenty-six months; 5 were alive and well fourteen to twenty-four months after operation.

Of the 17 patients operated on in the last three years after the prostate gland was definitely cancerous to palpation, 6 were dead, 4 were alive but had recurrence (at sixteen, twenty-three, twenty-five and thirty months respectively); and 4 were alive and well fifteen to twenty-four months after operation.

Prostatitis.—Wesson [46] stated that infection of the prostate gland and seminal vesicles should be considered as one disease, because any condition involving the one almost invariably involves the other.

Acute prostatitis is generally caused by urethral instrumentation, by acute nonspecific urethritis or by cystitis. Chronic prostatitis is as frequent as chronic tonsillitis. It is a pyogenic infection originating in direct extension from the urethra or in invasion through the blood stream or the lymphatic vessels.

46. Wesson, M. B.: Symptoms of Non-Venereal Acute and Chronic Prostatitis, J. Urol. **39**:135-144 (Feb.) 1938.

Symptoms of prostatitis and seminal vesiculitis have been aptly described as pus, pain and rheumatism. A patient who has a pain in the lower part of the back or a pain in the groin, extending suprapubically toward the midline, below the umbilicus or down into the scrotum, who has a prostate gland and seminal vesicles that are nodular and indurated on palpation, whose prostatic secretion contains pus and dead spermatozoa and who complains of exacerbation of the pain on massage does not have a beginning hernia or "sacroiliac slip." He has a prostatic backache.

Prostatitis usually does not cause sexual disturbances, but it may be responsible for every phase of derangement, from mild inaptitude to complete impotence.

Pain may be local or referred. It may be only a sense of discomfort, an ache, a dull sensation of soreness, a stiffness, a burning sensation, a tired feeling or a "bearing down," or dragging, sensation. Perineal, testicular and anal pain is present in some degree in practically all cases; usually there is thickening of the vas deferens and infiltration of the epididymis. Frequently there is a complaint of fulness, itching and burning about the anal orifice. Because of the close relation between the seminal vesicles, the ureters and the peritoneum, abdominal symptoms are frequent.

Intestinal obstruction alleged to be secondary to pressure of swollen seminal vesicles but probably caused by an adynamic ileus has been reported. Pressure on the ureters by the inflamed vas deferens or seminal vesicles customarily results in symptoms usually associated with the presence of stones and strictures.

Haven [47] stated that chronic pyogenic prostatitis can be a focus in producing ocular inflammations of nonspecific, endogenous origin. A focus of infection produces an endogenous lesion of the eye. It may be due to the transfer of bacteria or of bacterial toxins. Recent experimental work indicates the possibility of involvement of an allergic phenomenon. The tonsils are more frequently foci of infection than are the sinuses.

Nonspecific lesions of the eye respond well to nonspecific shock therapy by the injection of milk, diphtheria antitoxin or triple typhoid vaccine. Endogenous ocular inflammation of nonspecific origin may be aggravated by too vigorous prostatic massage. Increase in ocular inflammation after prostatic massage is diagnostic, indicating that the prostate gland is the focus of infection.

One sterile prostatic smear does not mean that chronic prostatic infection is not present. Chronic pyogenic prostatitis is oftener of

47. Haven, W. K.: The Relationship of Lesions of the Nose, Throat, Accessory Sinuses and the Eye to Chronic Pyogenic Prostatitis, J. Urol. **39**:128-134 (Feb.) 1938.

hematogenous than of urinary origin. Chronic pyogenic prostatitis responds more readily to local treatment after all foci are eliminated, including those in the tonsils and sinuses.

In discussing the causes of chronic prostatic infection, Cumming and Chittenden [48] stated that 98 per cent of their patients have one or more definite foci of infection.

In general, their treatment is based on cultural and serologic investigations and, except in determination of the use of palliative measures, the prostate gland is a secondary consideration. If tonsils or tags left after tonsillectomy harbor antigenic organisms, their removal is imperative, regardless of the age of the patient. The nasal sinuses if infected are treated. Devitalized teeth are extracted, and peridental infection requires accurate eradication.

The intestinal tract is often a major focus of infection.

Cumming and Chittenden concluded that much of the direct treatment administered to the prostate gland is unsound and unwise. Heat applied in any form to the rectum is comforting to the patient but otherwise is of questionable value. Routine prostatic massage, irrigations and endoscopic applications of silver nitrate fall into much the same category. Intraprostatic injections of mercurochrome, of hypertonic saline solution and of whole blood have been unsatisfactory in the experience of the authors, and the experimental work of O'Conor and Ladd has made them realize more fully the dangers of this method.

At first there was a tendency to consider the staphylococci as contaminants in the prostatic secretion, but now they have assumed a dominant position, and every effort is made to eliminate such organisms. If staphylococci are present, the patient is given a course of three to six intravenous injections of neoarsphenamine. Recently, the authors have begun to use antistaphylococcus serum in small doses (1 to 2.5 cc.) at intervals of five or six days until a total dose of about 5,000 units has been given. If colon bacilli are found in the urinary or prostatic cultures, mandelic acid is administered. If antigenic streptococci (either hemolytic or nonhemolytic) are present, the patient is given sulfanilamide.

Cumming and Chittenden considered five factors as their criteria of "cure": (1) complete relief of symptoms, (2) normal cytologic character of the prostatic fluid, (3) sterile cultures and smears of the prostatic fluid, (4) satisfactory removal of all infected foci, and (5) normal or relatively normal antibody patterns.

About 75 to 80 per cent of patients may be relieved, at least temporarily, by some form of treatment, especially by rectal heat therapy.

48. Cumming, R. E., and Chittenden, G. E.: Pyogenic Prostatitis: A Clinical Analysis of the Immune Response, J. Urol. **39**:118-122 (Feb.) 1938.

In the remainder, symptoms may persist despite every therapeutic measure. In the author's series the patients have been relieved of symptoms in 90 to 95 per cent of cases.

Reversion to a cytologically normal and culturally sterile prostatic fluid is often difficult to obtain and is usually impossible without complete and satisfactory removal of the toxic foci.

Prostatic Injection.—Lovelace and Emmett [49] reported their experience with the injection of sylnasol into the left lateral lobe of the prostate gland in 8 dogs. Sodium psylliate (sylnasol) is a solution frequently employed for treatment of inguinal hernia by injection. In each case, approximately 6 cc. of the solution was injected into the left lobe of the prostate gland and divided among three sites of injection. Injection was not made into the right lobe; this served as a control. Two dogs were examined eight hours after the injection, and the remainder were examined at periods varying from two to twelve months after the injection. Evidence of urinary obstruction was not found, and symptoms did not occur. The prostate glands removed eight hours after the injection revealed definite small areas of necrosis where the sodium psylliate was injected. In each of the remaining prostate glands removed there was striking reduction in the size of the lobe into which the solution had been injected. In each instance the left lobe was approximately one-half to one-third the size of the right lobe. Evidence of loss of tissue was not found, and the reduction in size seemed to be associated with an increase in the connective tissue stroma.

Changes After Operation.—Zide [50] examined microscopically the tissue removed in 85 cases of benign prostatic hypertrophy in which two or more transurethral or suprapubic operations had been performed at the Mayo Clinic at intervals of three months or more. This study was undertaken for the purpose of determining whether operations on the prostate gland have any histologic effect on the portion of the gland that remains. In 11 of the 85 cases the initial operation had been suprapubic prostatectomy, and in the remaining 74 cases transurethral resection had been performed. The shortest interval between the first and second operation was three months, and the longest, sixteen years. Practically all of the transurethral resections were performed with the Braasch-Bumpus instrument. The tissue obtained was studied from the point of view of infection, malignancy and changes in character and amount of parenchyma, smooth muscle and fibrous stroma.

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49. Lovelace, W. R., and Emmett, J. L.: Intraprostatic Injection of Sclerosing Solutions: An Experimental Study, Proc. Staff Meet., Mayo Clin. **13**:196 (March 30) 1938.

50. Zide, H. A.: Changes in Prostatic Tissue After Operation, Proc. Staff Meet., Mayo Clin. **12**:269-272 (Dec. 8) 1937.

Zide arrived at the following conclusions: 1. Evidence of a carcinomatous tendency in the remaining prostatic tissue after transurethral resection greater than that following suprapubic enucleation is not apparent. In none of his series of cases were signs of malignant change found. 2. The incidence of prostatitis occurring after transurethral resection is not high. 3. In the majority of cases the prostatic tissue removed because of recurrent obstruction resembled closely that obtained at the primary operation, regardless of whether suprapubic enucleation or transurethral resection had been performed.

BLADDER

Tumor.—Cabot and Pace [51] discussed the treatment of patients with extensive cancer of high malignancy in the bladder and patients with large malignant lesions of low grade for which transurethral treatment is inadequate. They emphasized the importance of accurate preoperative data as the most valuable aid in determination of the exact type of operative treatment best suited to each patient. Because of the wide variety of surgical procedures that may be carried out, it is important to determine as accurately as possible what procedure is indicated. This is often difficult, because preoperative data are not always entirely accurate. Estimation of the size and position of the tumor depends on the experience of the cystoscopist to a large extent, and it is always difficult to determine cystoscopically the extent of involvement of the deeper layers of the bladder and the ureters. Likewise, it is difficult to determine preoperatively whether or not the lesion has extended through the wall of the bladder and has involved the adjacent structures. There are three main preoperative diagnostic measures which should be utilized in every case, namely: (1) cystoscopic examination, (2) cystographic examination and (3) intravenous urographic examination.

Cabot and Pace based their observations on 46 cases in which suprapubic operation for vesical neoplasm had recently been performed at the Mayo Clinic. Cystoscopic examination is of importance in determination of the presence of the tumor and also (by removal of appropriate specimens) of the type, grade, position and extent of the lesion. It is particularly useful in determination of the situation of the mass in relation to the ureters and to the vesical neck. Diagnosis from cystoscopic biopsy is not invariably accurate; however, with rare exceptions, the grade and type of lesion as determined by biopsy are observed in subsequent pathologic examinations to be remarkably accurate. In the group of 46 cases reviewed, opinions formed at the time of cysto-

51. Cabot, H., and Pace, J. M.: Methods of Selecting the Proper Operative Treatment for Cancer of the Bladder, Tr. Am. A. Genito-Urin. Surgeons **30**: 235-248, 1937.

scopic study were almost precisely correct in 26, more or less incorrect in 19 and vague in 1, when judged by the findings at suprapubic exploration.

The cystogram is most helpful in estimation of the extent of vesical involvement as shown by filling defects. In a certain number of cases a cystogram is suggestive of considerably more extensive involvement than would be noted from cystoscopic examination. Again, it may be helpful in the presence of a massive, pedunculated tumor of low grade, when an accurate cystoscopic estimate cannot be made of actual involvement of the vesical wall. Unfortunately, examination of the cystogram does not indicate in which cases the lesion has extended into the perivesical tissues and in which it is still confined to the vesical wall.

An intravenous urogram is of most value in demonstrating the presence or absence of obstruction to one or both ureters and the resultant effects of such obstruction on renal function. Obstruction of the ureters cannot be accurately determined in every case by cystoscopic examination, and an intravenous urogram is of inestimable value for this purpose. The use of intravenous urographic study also eliminates the necessity of catheterizing the ureters, which is not always possible or desirable.

Summarizing their opinions, Cabot and Pace concluded that cystoscopic study with the obtaining of appropriate material for pathologic study and the taking of an intravenous urogram are essential diagnostic measures in cases of vesical neoplasm. The retrograde cystogram is given second place in diagnosis, although its use is generally desirable. A classification of treatment follows.

1. Suprapubic treatment. Transvesical electrocoagulation is best suited to a bushy, papillomatous tumor of low grade, classified according to Broders' method as of grade 1 but often regarded as benign. It may also be applicable to a small sessile tumor classified as of grade 1 or 2, in which case it should generally be combined with implantation of radon.

Electrocoagulation is a purely palliative method of treatment for inoperable tumor and is used to control hemorrhage. The use of this method has been fairly widespread in the past. The authors expressed doubt as to whether it will remain a recognized treatment.

2. Implantation of radon. This measure, with or without preliminary or postoperative irradiation, has a definite place in the treatment of vesical tumor, but it is difficult to select cases in which its use is suitable. It is suitable for application to a tumor of high grade. It is important to determine whether the tumor to be treated with implantation of radon encroaches on the ureter, because such treatment should rarely, if ever, be applied if the ureter is grossly obstructed or if an extensive lesion exists.

3. Excision or segmental resection. "Excision" means removal of a circumscribed portion of the vesical wall. "Segmental resection" is defined as removal of a larger or smaller segment of the vesical wall, a suprapubic opening being used and resection being extended downward and laterally as far as necessary. Excision gives good results in cases in which there is little or no involvement of the deeper layers of the vesical wall and in which the lesion is relatively small. Segmental resection gives the best results in the treatment of a tumor of the vesical dome or of the lateral vesical wall.

4. Transplantation of the ureters to the bowel or to the skin. This type of operation is done either as a procedure preliminary to total cystectomy or as a palliative measure in cases of obstruction of both ureters. In the latter instance it may be followed by irradiation. Cabot and Pace concluded that ureteroenterostomy should be confined to cases in which gross abnormality of the ureters does not exist. Total cystectomy should be done in two stages, the ureters being transplanted to the intestine at the initial operation and the bladder being removed at the second. Cutaneous ureterostomy is largely reserved for patients with dilated ureters. The authors concluded that this operation has a wider scope of usefulness than has been realized in the United States. The records of 9 illustrative cases of vesical neoplasm were abstracted by the authors.

Randall and Uhle [52] stated that the treatment of vesical carcinoma should be selective. Transvesical diathermy is of value in treatment of a lesion involving only the basal regions of the bladder or a lesion not amenable to vesical resection or to transurethral management.

The safety of transvesical diathermy is shown by an operative mortality rate of 9.8 per cent.

The three most important complications of the use of diathermy are: (1) establishment of a fistulous communication between the bladder and the rectum or vagina, (2) acute pyelonephritis, and (3) chronic pyelonephritis. A fistula can be prevented by curbing the overzealous application of current of high frequency. There was only 1 fistula (vesicovaginal) in Randall and Uhle's series. The incidence of acute pyelonephritis can be reduced by introduction of a ureteral catheter for drainage at the conclusion of the operation if diathermy has been applied directly over the ureteral orifice or in close proximity to it. Stenosis of the ureteral orifice, secondary to healing and fibrosis, is a later manifestation of the effects produced by surgical diathermy. Renal morbidity (chronic pyelonephritis) can be lessened by periodic ureteral dilation during the patient's convalescence.

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52. Randall, A., and Uhle, C. A. W.: Transvesical Diathermy in the Treatment of Carcinoma of the Bladder, Surg., Gynec. & Obst. **66**:927-932 (May) 1938.

Diathermy produces aseptic necrosis. If infection supervenes, the progression of pathologic events may range from the simple to the fulminating type, with pelvic cellulitis, pelvic phlebitis and death.

Cicatricial reaction following diathermy does not produce great vesical deformity. In spite of extensive diathermy, scarring is often minimal, and in 47 per cent of cases vesical comfort can be acquired.

There was a general mortality rate of 56.8 per cent. Death was ascribed to recurrence of the growth, with secondary renal infection and uremia. No evidence of recurrence, irrespective of the length of follow-up, was found in 35.3 per cent of cases. Recurrent growths developed in 43.1 per cent.

Routine cystoscopic study after operation is of great importance in detection of early or late recurrence. In 1 instance a papillary recurrence was found seventy-four months after the original operation. Cystoscopic fulguration is sufficient to effect control.

The importance of an efficient follow-up service cannot be overemphasized. Ten patients (19.6 per cent) were followed for forty to eighty-six months. Four had recurrences, and 6 were free of recurrence.

Randall and Uhle have been unable to substantiate the figures of Counseller and Braasch (88 per cent of patients living more than five years), but they felt that the results of diathermy in the treatment of carcinoma of the bladder are significant and should foster a wider clinical interest in this method of treatment.

Exstrophy.—Gaudin and Cabot [53] reported the case of a boy aged 1 month who had a small pedunculated tumor covered with mucosa. The tumor was situated in the midline, just above the symphysis pubis. It was spherical, red and glistening and was surrounded by skin which showed some evidence of irritation. There was no obvious drainage from the mass, which was soft and seemed slightly movable on the subjacent abdominal wall. The child urinated normally. Except for the tumor, no congenital abnormality was noted. The growth was removed by simple excision. There was no evidence of continuation of the mass into the interior, and it extended downward only to the subcutaneous tissue. The postoperative course was uneventful. Microscopic examination of the tissue removed showed it to be a portion of the bladder. Gaudin and Cabot discussed the embryologic considerations that enter into partial exstrophy of the bladder. They concluded that the difference between the anatomic conditions in the case presented and total extraversion of the bladder, with epispadias, is a matter only of degree of abnormality.

53. Gaudin, H. J., and Cabot, H.: Partial Exstrophy of the Bladder: Embryologic Considerations; Report of a Case, Proc. Staff Meet., Mayo Clin. **13**:216-220 (April 6) 1938.

Cystitis Emphysematosa.—Wells [54] reported the results of 1,800 necropsies. He observed 7 typical cases of cystitis emphysematosa. He stated that he has no evidence that either glycosuria or vesical trauma is an essential factor in the production of this condition, although one or the other factor is present in many cases. In 5 of the 7 cases reported the patients were males. Wells' observations indicated that postmortem formation of gas is probably not responsible for this condition but gave no suggestion as to when or how it is usually produced. If cystitis emphysematosa is really much more frequent now than formerly, it may be owing to the greater frequency of vesical trauma from cystoscopy and catheterization or from the greater frequency of glycosuria in terminal states from therapeutic injections of dextrose. It probably has no important influence on the course of the patient's condition.

Decompression.—The idea that sudden emptying of the chronically distended bladder is dangerous is firmly established in the literature. Creevy [55] stated that the theories explaining such a danger fail to withstand critical analysis because at necropsy, in the absence of residual urine, lesions ascribable to sudden empyting of the chronically distended bladder cannot be distinguished from those due to infection. Eighty per cent of patients who die after catheterization succumb to pyelonephritis, either acute or chronic; 20 per cent succumb to infections outside the urinary tract. Sudden death after catheterization may be due to coincidental coronary thrombosis or to pulmonary embolism. The phenomena usually ascribed to sudden emptying of the bladder can be produced by pyelonephritis. Gradual decompression of the distended bladder did not reduce the mortality in a series of 120 cases as compared with that in a similar series in which sudden emptying was practiced. Gradual decompression should be abandoned. Its abandonment has not produced any untoward reactions in Creevy's experience.

Incontinence.—Meschede [56] recommended two operative procedures for the cure of traumatic incontinence in women; both gave him satisfactory results. For elderly women he used an operation involving interposition of the uterus; for younger women or hysterectomized women he used a plastic procedure with both bulbocavernous muscles and strips of fascia from the pyramidalis muscle. In this procedure muscles and fascia form a tight ring around the urethra. Meschede has been satisfied with his results to such an extent that he now uses these two methods in all cases.

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54. Wells, H. G.: Report of Seven Cases of Cystitis Emphysematosa, J. Urol. **39**:391-397 (April) 1938.

55. Creevy, C. D.: Is Sudden Emptying of the Chronically Distended Bladder Dangerous? J. Urol. **39**:403-409 (April) 1938.

56. Meschede, H.: Zur Behebung der traumatischen Inkontinenz der Frauen, Ztschr. f. urol. Chir. u. Gynäk. **44**:22-25 (March 3) 1938.

Presacral Neurectomy.—Pearl and Strauss [57] stated that presacral neurectomy may establish voluntary micturition in cases of neurogenic vesical dysfunction with retention, in which there are weakness of the detrusor muscle and spasticity of the internal sphincter. However, the detrusor muscle may remain hypotonic, and the bladder may not empty completely.

Presacral neurectomy increases the expulsive force of the detrusor muscle and relaxes a spastic internal sphincter. This effect may be temporary.

Bilateral sacral ganglionectomy is advisable in addition to presacral neurectomy in the treatment of painful vesical conditions or when prolonged vasodilatation is desired in cases of severe, intractable cystitis. Undesirable effects have not been noted following presacral neurectomy and sacral ganglionectomy. At present, operations on the sympathetic nerves supplying the bladder should be considered experimental.

TESTICLE

Tumor.—Hinman and Powell,[58] in discussing the management of tumor of the testicle, pointed out that examination of the scrotal mass suspected of being a tumor should be carried out with a minimum of handling and squeezing. The test for gonadotropic substance aids materially in diagnosis. A negative result from the test, however, does not exclude the possibility that the tumor is malignant, because in about 20 per cent of the authors' cases urinary excretion of the gonadotropic substance did not occur. The danger of squeezing cells of a malignant tumor into the lymphatics is far greater at the time of examination than at orchidectomy when the operation is properly carried out through a high inguinal incision. The cord may be clamped and divided, all the lymphatic and vascular channels leading from the neoplasm being severed, before the neoplasm is handled. When the mass is removed, it should be examined for gonadotropic substance; information gained from such an examination, together with that from histologic examination and the previous urinary gonadotropic titer, makes it possible to classify the neoplasm, determine the prognosis and outline the extent of further treatment. It is also of aid in deciding whether such treatment is to be surgical, roentgenologic or both.

Hinman and Powell classified a group of neoplasms of the testicle from a glandular-histologic point of view into certain main types: embryonal mixed cell tumor (teratoma), embryonal carcinoma (uni-

57. Pearl, F. L., and Strauss, B.: Presacral Neurectomy and Sacral Ganglionectomy in Affections of the Bladder, J. Urol. **39**:645-661 (May) 1938.

58. Hinman, F., and Powell, T. O.: The Management of Tumor of the Testicle, J. A. M. A. **110**:188-190 (Jan. 15) 1938.

cellular) and the rare, nonembryonal and miscellaneous tumors. In an analysis of 58 cases in which tests for gonadotropic principle were made, there were 14 cases of embryonal teratoma. Only 1 patient lived five years. The response to irradiation in these cases was fair, but the prognosis as determined from the result obtained was extremely poor. There were 33 cases of embryonal carcinoma. In 7 of these the growths were regarded as primitive tumors causing high urinary gonadotropic excretion. In this group the response to irradiation was good, but only 2 patients lived two years after irradiation. The remaining embryonal carcinomas (histologically "seminomas") were regarded as examples of differentiated embryonal carcinoma and caused excretion of small amounts of gonadotropic substance. In this group of 26 cases the response to irradiation was good, and 22 of the patients were alive and apparently well at the time of the report, three to four years after irradiation. The prognosis in this group is regarded as good. There were 3 cases of benign adult teratoma. There were 8 cases of the same histologic description as the differentiated type of carcinoma, but in these there was no urinary gonadotropic excretion, and when the tumors were extracted it was shown that they were entirely void of the gonadotropic principle. These were considered as nonembryonal or adult tumors and were classified as "adult seminoma." There were 8 such tumors; only 1 patient was dead at the end of three years.

Two cases of tumor associated with unusually high urinary gonadotropic titer were reported. In both cases the gonadotropic titer of the urine reached 1,000,000 units per liter. The tumor in each case was regarded as primitive embryonal teratoma (chorioepithelioma). In both cases heavily filtered irradiation at 850 kilovolts was given. The patients lived about one year after the apparent onset of the disease.

Ferguson [59] disagreed with Hinman and Powell on the point of orchidectomy before irradiation. He conceded that the scientific information to be obtained by microscopic examination of the unaltered tumor and by assay of fresh tissue for gonadotropic substance is an advantage. However, this advantage carries little weight when it is seen that the clinical results obtained at the end of five years are better when irradiation precedes orchidectomy. In a review of the Memorial Hospital series of 292 teratomas of the testis, encountered between 1917 and 1929, it was found that of 14 patients who had primary operable tumors and were treated by irradiation before orchidectomy, 11 (78.5 per cent) were alive and without evidence of disease at the end of five years, whereas of 28 patients who had primary operable tumors and

59. Ferguson, R. S., in discussion on papers by Kreutzmann and Colloff, Hinman and Powell and Fetter, J. A. M. A. **110**:196-197 (Jan. 15) 1938.

on whom orchidectomy was performed before irradiation was given, only 12 (42.8 per cent) were alive and well without evidence of disease at the end of five years.

Ferguson admitted that with immediate irradiation after orchidectomy there may not be any difference in the results at the end of five years as compared with the results of irradiation before orchidectomy, but he stated that at present he feels that the advantage lies with preoperative irradiation.

EPIDIDYMIS

Tumor.—Lazarus [60] stated that primary malignant tumor of the epididymis is rare, there being but 40 cases on record. Although such tumors have been classified under a variety of names, it seems that the majority of them, if subjected to an extremely critical analysis, would fall in the group of malignant teratoma in which one type of cell predominates to the exclusion of all other teratomatous elements. Summarizing the cases according to the authors' designations of the tumors, one finds 20 carcinomas and 17 sarcomas. Seventy-eight per cent of patients who stated the duration of their illness had had symptoms for longer than a month before they sought medical aid. Although 16 patients in this series did not mention pain, 75 per cent of the remaining patients had a definite history of pain either preceding or accompanying swelling in the testis. Only 15 of the 40 patients gave information concerning trauma, and 10 of these 15 patients stated that trauma had definitely antedated the appearance of the tumor.

Simple orchidectomy appears to have been the procedure of choice in the vast majority of collected cases. Lately, irradiation has been advocated as a valuable adjuvant to surgical management.

Regarding results, the survey lacked information concerning this feature in 10 cases. In the remaining 30 cases, 40 per cent of the patients were reported dead within two years of operation, and 27 per cent died within the first year.

INFECTIONS OF THE VAS DEFERENS

Kreutzmann [61] stated that viable organisms may be present in the vas deferens without causing symptoms or producing gross changes. Epididymitis following ligation of the vas deferens is due to lighting up of a previous vasal infection and not to infection of the lymphatic vessels or the blood stream. Vasitis and epididymitis occur only in the presence of infected urine. Under certain conditions, reflux of urine

60. Lazarus, J. A.: Primary Malignant Tumor of the Epididymis, J. Urol. **39**:751-765 (June) 1938.

61. Kreutzmann, H. A. R.: Studies of Infections of the Vas Deferens, J. Urol. **39**:123-127 (Feb.) 1938.

may occur into the vas deferens as it does into the ureter. When the urine is infected, instrumentation doubles the probability of epididymitis. Chronic prostatitis alone will not cause vasitis or epididymitis.

EPISPADIAS

Cabot [62] emphasized the fact that the number of different operations suggested for the correction of epispadias and hypospadias attests the lack of complete success with any one procedure. He described the technic for correction of epispadias either associated or unassociated with exstrophy. Correction of this abnormality has been difficult because of the partially separated corpora cavernosa. This condition often involves considerable tension when the urethra is formed from lateral flaps taken from the sides of the corpora, and failure may result.

Cabot discussed the disadvantages of certain procedures for correction of epispadias and then described a technic with his own modification. The urethra is constructed from the mucous membrane covering the dorsal surface of the penis. In order to provide a covering of skin for this newly formed canal, two transverse incisions are made in the scrotum, one at the penoscrotal juncture and one farther posteriorly. A tunnel of scrotal skin is thereby created, and the penis is inserted beneath it so that the flap of scrotal skin lies over the dorsal surface of the penis, where the new urethra has been formed. The penis should be left in this position for at least two or three weeks, at the end of which time the scrotal flap may be divided and the wound united in the midline of the scrotum by suture. Cabot's article is well illustrated by drawings.

SPERMATOCELE

Huggins and Noonan [63] stated that spermatocele arises as a result of partial obstruction of the sperm-conducting system and that vasotomy does not cause increase of its size. Spermatocele always contains spermatozoa and does not appear before puberty. The membrane is impermeable to phosphate in the direction from the plasma to the cyst and is permeable with difficulty in the opposite direction.

In the authors' cases, spermatocele always disappeared after application of roentgen therapy, without a significant decrease in the size of the testis and without loss of sexual potency or libido. With the doses used, 4 patients had spermatocele sixty days after treatment, and a second course of treatment was given, but this always was sufficient to

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62. Cabot, H.: Treatment of Epispadias in the Male, Proc. Staff Meet., Mayo Clin. **12**:793-795 (Dec. 15) 1937.

63. Huggins, C., and Noonan, W. J.: Spermatocele, Including Its X-Ray Treatment, J. Urol. **39**:784-790 (June) 1938.

make the lesion recede permanently. Because sterilization occurs, roentgen therapy is advised only in case sterility is not undesirable, as when the patient is old.

UROGENITAL INFECTIONS

Anaerobic infection complicating surgical procedures on the urinary tract is infrequent. Yet the development of this type of infection is of such serious moment as to warrant emphasis of the importance of its early recognition and treatment. Mencher and Leiter [64] gave abstracts of 14 cases of postoperative anaerobic infection of the urinary tract, observed at the Mount Sinai Hospital, New York, during the past eleven years. Infection in 11 cases was due to Bacillus welchii, and in 3 cases typical symptoms of tetanus occurred.

The occurrence of postoperative anaerobic infection has always given rise to theoretic discussions as to the portals of entry. The following sources of contamination are to be considered: (1) the skin, (2) the rectum, (3) operative materials, and (4) urine, pus and urinary calculi.

The prognosis in cases of infection by B. welchii is directly dependent on early recognition and adequate treatment. If there is an inordinate rise in temperature, with or without symptoms of toxemia, careful inspection of the wound in addition to a general physical examination should be done. Discoloration, edema or crepitation in the region of the wound calls for further investigation of its depths. Crackling may be heard if firm pressure with the stethoscope is applied against the involved region in which gas is present.

Mencher and Leiter stated that under these circumstances they remove superficial and deep sutures, watching for serum, pus and air bubbles. Smears and cultures are immediately made, and if these yield bacteria, active therapy to combat the infection is instituted. The wound is split wide open, tubes and catheters are placed in the depths for continuous irrigation with hydrogen peroxide and oxygen, and large quantities of polyvalent Bacillus perfringens serum are administered intramuscularly, locally and even intravenously.

When the infection subsides, the use of diluted solution of sodium hypochlorite U.S.P. may be alternated with that of irrigations with hydrogen peroxide to hasten the separation of necrotic tissue and to stimulate the process of granulation.

Early recognition of tetanus is more difficult. General symptoms signify late manifestations of the disease. The appearance of the wound is not of aid in making the diagnosis. The mortality in cases of tetanus

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64. Mencher, W. H., and Leiter, H. E.: Anaerobic Infections Following Operations on the Urinary Tract, Surg., Gynec. & Obst. **66**:677-683 (March) 1938.

is appalling. Any hope of combating the complication depends on early diagnosis and administration of large doses of tetanus antitoxin by all routes.

Helmholz [65] stated that coccic infection occurs with equal frequency in the male and in the female. Bacillary infection of the female occurs three to four times as frequently as bacillary infection of the male. Coccal infection occurs by way of the blood stream, whereas bacillary infection occurs by other routes. The impossibility of infecting the normal bladder of man by introduction of bacteria through the urethra has its counterpart in inability to produce experimental infection of the bladder of the rabbit by injection of massive doses of bacteria. The greater frequency of bacillary infection in the female would lead to the belief that the infection occurs by way of the urethra, and although lymphogenous infection must be considered a possibility, there is no definite proof of its occurrence. At present it is impossible from study of material relevant to human beings to give any definite answer to the question. However, it is evident that two factors are necessary to cause infection of the bladder, namely, lowered resistance of the mucosa and bacterial invasion.

Experimental production of infection of the renal pelvis from the bladder has been accomplished by intracystic injection of bacteria into the bladder. The histologic picture of pelvic inflammation differs from that seen when the pelvis is infected by way of the blood stream. Histologic studies of the ureter have shown that in only 3 of 13 cases was there any evidence of periureteral inflammation. Therefore, unless it is assumed that infection can be spread by way of the periureteral lymphatic structures without leaving a trace behind, it must be assumed that in the other 10 cases the infection was spread by way of the lumen of the ureter. The same conclusion must be drawn concerning spontaneous pyelitis in rabbits, in which evidence of periureteral infiltration was found in only 6 of 16 cases. Taking this in conjunction with the work of David, which showed that periureteral inflammation does not necessarily mean that infection of the renal pelvis is present, Helmholz has assumed until more definite information is available that the usual spread of infection from the bladder to the pelvis is by way of the lumen of the ureter.

With stasis, the parenchyma of the kidney rapidly becomes infected from the pelvis by way of the perivascular lymphatic structures and by direct passage of the organisms through the pelvic lining over the parenchyma. Thrombosis forms an important feature of the renal

65. Helmholz, H. F.: Ascending Infection of the Urinary Passages, Am. J. Surg. **38**:18-28 (Oct.) 1937.

changes. Without stasis, infection of the pelvis tends to remain local, and only exceptionally does infection spread to the parenchyma by the same channels.

The striking difference between the two series of experiments would indicate that stasis is the all-important factor in producing ascent of infection from the renal pelvis to the renal parenchyma.

Nelson [66] stated that experimental and clinical findings justify the conclusion that cervical infection can and often does extend to the urinary tract. When the trisymptom complex to which reference has been made is present, the clinician should suspect cervicitis to be the primary cause of such symptoms. Infection in the deep portion of the cervix is sometimes not discernible to inspection or palpation. Cauterization usually fails to arrest extension of the infection from the cervix to the urinary tract. When properly performed for cervicitis that is causing urinary symptoms, the Sturmdorf type of operation usually brings about permanent relief.

Vest, Harrill and Colston [67] stated that administration of sulfanilamide is the most important forward step yet taken by scientific medicine in the treatment of gonorrhea and other urinary infections.

Sulfanilamide itself may be only the first of many efficacious and satisfactory new compounds, but with the vast problems yet to be elucidated concerning this drug, years will undoubtedly be required to produce results such as Ehrlich predicted. From research in all fields, chemical, biologic and clinical, there will undoubtedly evolve the ideal remedy as postulated by Ehrlich in 1913: "A remedy entirely innocuous in itself, which is not fixed by the organs of the body but which would, however, strike the parasites with full intensity."

Schulte [68] reviewed the literature on the development of sulfanilamide, which, he stated, is the product of numerous investigations extending over a period of thirty years. Domagk is given credit for the discovery of "prontosil," and Gelmo was the first to mention the drug now called sulfanilamide. Many other physicians contributed largely to the chemical developments which permitted the synthesis of these drugs. At present, a number of investigators are engaged in the further study of various compounds that might be used for chemotherapy.

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66. Nelson, O. A.: Urinary Tract Disturbances Referable to Cervicitis, J. Urol. **39**:361-365 (March) 1938.

67. Vest, S. A.; Harrill, H., and Colston, J. A. C.: The Use of Sulfanilamide in Urogenital Infections, J. Urol. **39**:198-221 (Feb.) 1938.

68. Schulte, T. L.: History of the Development of Sulfanilamide (Para Amino Benzene Sulfonamide), Proc. Staff Meet., Mayo Clin. **13**:53-60 (Jan. 26) 1938.

Helmholz [69] stated that mandelic acid and sulfanilamide are two valuable drugs which have been made available during the past few years for the treatment of urinary infections. Mandelic acid is dependent for its action on a concentration in the urine greater than 0.5 per cent and a p_H of the urine less than 5.5, so that it is not likely to be successful unless the function of the kidney is normal or nearly so. If the urine does not reach the necessary p_H of 5.5, ammonium nitrate may be given in addition. The usual adult dose of ammonium mandelate is 12 Gm. daily. The output of urine in twenty-four hours should be kept at approximately 1,000 cc. Acidification of urine can be tested by the patient with the use of chlorphenol red. Proper acidity is indicated by yellow and insufficient acidity by red. It may also be tested by nitrazine paper, and the proper acidity is indicated by yellow. Insufficient acidity is indicated by green.

Mandelic acid is effective against all the common gram-negative bacilli, against Staphylococcus aureus and against Streptococcus faecalis. It is less useful in the treatment of infections caused by urea-splitting organisms, such as those of the Proteus group.

Helmholz has demonstrated that with sulfanilamide in concentrations easily obtainable by oral administration of the drug the urine is bactericidal for Staph. aureus, Escherichia coli, Aerobacter aerogenes and organisms of the Proteus and Pseudomonas groups. It does not, however, destroy Str. faecalis. Sulfanilamide is more effective in alkaline than in acid urine. This is of definite significance in the treatment of infections with Proteus.

Helmholz reported 2 cases of infection caused by Esch. coli and A. aerogenes respectively in which the infection yielded rapidly to administration of sulfanilamide after long and unsuccessful treatment with mandelic acid. The author concluded that sulfanilamide is the remedy of choice in the average case because of its ease of administration, its tolerance by the stomach and the fact that it can be used during the acute stage of the disease. It should not be used in the treatment of infections caused by Str. faecalis. Mandelic acid and sulfanilamide are used satisfactorily to supplement each other. The dose of sulfanilamide is 5 to 10 grains (0.32 to 0.65 Gm.) a day for infants and 20 to 30 grains (1.29 to 1.94 Gm.) a day for children 8 to 12 years of age.

ROENTGENOLOGY IN UROLOGY

Junker [70] described the results of his new method of roentgenologic diagnosis for surgical diseases of the kidney. He adapted to urologic

69. Helmholz, H. F.: A Comparison of Mandelic Acid and Sulfanilamide as Urinary Antiseptics, J. A. M. A. **109**:1039-1041 (Sept. 25) 1937.

70. Junker, H.: Fortschritte der chirurgischen Nierendiagnostik, Ztschr. f. Urol. **32**:112-128 and 191-207, 1938.

practice Berg's method of roentgenologic diagnosis of gastric lesions. After intravenous injection of skiodan a preliminary roentgenogram is made, and subsequently a series of roentgenograms of interesting details. This method offers striking advantages over ordinary pyelographic or pyeloscopic examination in detection of small but important changes. Anatomic changes of the calices, dysfunction of peristalsis in the calices and ureters, early changes in cases of tuberculosis and ascending pyelitis and the anatomic substratum of "essential" hematuria can be demonstrated clearly.

Excretory urograms of 27 normal pregnant women throughout the succeeding months of gestation and the puerperium showed varying degrees of dilatation of one or both ureters and renal pelves in every patient. The right kidney was more affected than the left, dilation of the ureter always began at the pelvic brim, and the pelvic portion was never significantly involved. The dilatation was progressive, reached its maximum several weeks ante partum and had disappeared by about the twenty-eighth day post partum. It occurred later (but was more severe) in primiparas than in multiparas. These findings were confirmed by anatomic and histologic studies of 13 parturient women, all but 2 of whom died at term.

In addition to dilatation of the ureters, great hypertrophy of the sheaths of Waldeyer at their lower ends was noted. There was a softening process in the wall of the abdominal portion of the ureter, the structure becoming flaccid and easily compressible. The growing uterus impinges on the ureter at the pelvic brim, especially the right, because its course over the iliac vessels differs from that on the left and makes it more susceptible to pressure. The dilatation which results can be diminished by the use of indwelling ureteral catheters if they are left in place longer than twenty-four hours. With the advance of pregnancy the excretion time of the kidney was greatly delayed, and lack of tone and decrease in rhythmic expulsive force of the dilated ureter were observed.

Hormonal activity contributes to the process of softening and atony of the ureter, which makes it susceptible to dilation from slight pressure.

A careful bacteriologic study of the urinary tracts of pregnant women as compared with those of nonpregnant women showed only a slight increase in the incidence of bacteria in the urine in the former.

Among 50 normal pregnant women, cultures of the urine from the bladder on brain broth mediums yielded bacteria in 64 per cent of cases, and cultures on blood agar mediums, in 36 per cent. Among 50 normal nonpregnant women, cultures yielded bacteria on brain broth mediums in 44 per cent and on blood agar mediums in 18 per cent of cases. Only 4 cultures yielding bacteria were obtained from the urine taken from the kidney among the 50 normal pregnant women.

Hundley's [71] analysis of 236 patients with inflammatory disease of the urinary tract admitted to the obstetric wards of the Maryland University Hospital showed that 136 were primiparas and 100 multiparas. The symptoms were more severe among the primiparas. The incidence of pyelitis of pregnancy was 3.1 per cent. Confirming the observation that pressure changes in the urinary tract are not observed until after the sixteenth week, only 11 patients had pyelitis during the first four months of pregnancy. The frequency increases as pregnancy advances. In the middle trimester there were 32 cases; in the last period, 97; and post partum, 96. Twenty patients were delivered spontaneously, whereas in 11 cases pregnancy was interrupted artificially.

Treatment consists of medicinal, or palliative, measures and operative, or radical measures. Of Hundley's 236 patients, all but 25 responded to palliative measures, such as increased intake of fluid, postural treatment, administration of urinary antiseptics, such as mandelic acid and sulfanilamide, and the ketogenic diet. The last-mentioned drug has been abandoned because it produces a great decrease in the carbon dioxide–combining power of the blood and involves a restriction of fluids.

Hundley's experience with mandelic acid has been disappointing, and he has been conservative in the use of sulfanilamide until more definite proof is available as to its harmlessness in pregnancy.

If after six or seven days of medicinal treatment the symptoms are not alleviated, cystoscopic and ureteral catheterization are performed and are repeated as often as necessary. If the response to simple catheterization is not satisfactory, the ureteral catheters are left in place for twenty-four to forty-eight hours, but not longer, because they are likely to induce labor. In 11 cases in this series it was necessary to empty the uterus.

UREMIA

Wear, Sisk and Trinkle [72] made an experimental and clinical study of peritoneal lavage in the treatment of uremia. With few exceptions, previous investigators have used saline solutions, dextrose solutions or a combination of these. The objectionable feature was that they removed not only nitrogenous elements but also such vital substances as calcium, chlorides and sugar. For this reason, Wear, Sisk and Trinkle chose lactate-Ringer solution for their first perfusion fluid.

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71. Hundley, J. M.; Siegel, I. A.; Hachtel, F. W., and Dumler, J. C.: Some Physiological and Pathological Observations on the Urinary Tract During Pregnancy, Surg., Gynec. & Obst. **66**:360-379 (Feb.) 1938.

72. Wear, J. B.; Sisk, I. R., and Trinkle, A. J.: Peritoneal Lavage in the Treatment of Uremia: An Experimental and Clinical Study, J. Urol. **39**:53-62 (Jan.) 1938.

The procedure was carried out with the patient under morphine and pentobarbital sodium anesthesia. For continuous perfusion two trocars were used. A standard gallbladder trocar was introduced in the upper portion of the abdomen. The trocar introduced into the lower portion of the abdomen was modified by the placing of numerous small holes in its distal third to avoid occlusion of a single opening by the omentum and intestines. From an insulated reservoir the fluid was introduced into the upper cannula. The lower cannula was attached to rubber tubing which hung dependent into a bottle on the floor and acted as a siphon. The perfusion fluid was kept at a temperature of 40 C. in a water bath. Specimens of blood were taken before and after the lavage, and specimens were taken from the fluid recovered from the lavage.

Decrease in concentration of nonprotein nitrogen of the blood after lavage ranged from 10 to 59 mg. per hundred cubic centimeters. The greatest reduction occurred in cases in which the highest retention of nitrogen was present.

Wear, Sisk and Trinkle stated that they do not offer peritoneal lavage as a treatment for patients who have hopelessly damaged kidneys, but they feel that it is a method well worthy of trial in cases in which there is some hope of return of renal function. The procedure itself is without morbidity or mortality, and large quantities of nonprotein nitrogen can be removed. The treatment of uremia by this method is the treatment of a secondary damaging factor. Every effort should be made to combat the severe decrease in the carbon dioxide–combining power of the blood which is a rather constant and dangerous result of uremia.